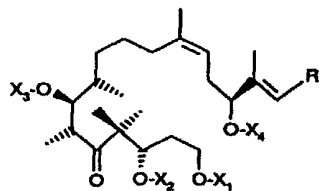


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(54) Title: INTERMEDIATES FOR THE SYNTHESIS OF EPOTHILONES AND METHODS FOR THEIR PREPARATION			
<div style="text-align: center;">  <p>(I)</p> </div>			
(57) Abstract  The invention relates to a method of synthesis for a compound of formula (I), wherein R is a heterocyclyl moiety and X <sub>1</sub> , X <sub>2</sub> , X <sub>3</sub> and X <sub>4</sub> are, independently of each other, protecting groups, which is appropriate for the synthesis of epothilone B and desoxyepothilone B.			

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## Intermediates for the Synthesis of Epothilones and Methods for their Preparation

### Summary of the Invention

The invention relates to a new method of synthesis of an intermediate useful for the synthesis of epothilone B and desoxyepothilone B and derivatives thereof, as well as to certain new partial reaction sequences for the production of key intermediates.

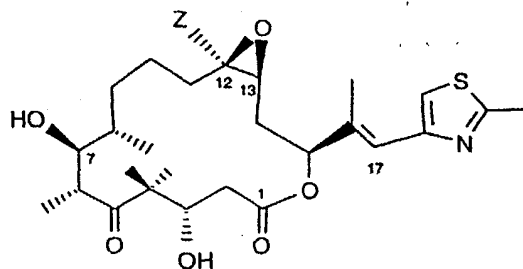
### Background of the Invention

Among cytotoxic agents for the treatment of tumors, Taxol® (Paclitaxel), a microtubule stabilizing agent, has become a very important compound with a remarkable economic success (see McGuire, W.P., et al., *Ann. Int. Med.* **111**, 273-9 (1989)).

Taxol® has a number of disadvantages. Especially its extremely low solubility in water represents a severe problem. It has become necessary to administer Taxol in a formulation with Cremophor EL® (polyoxyethylated castor oil; BASF, Ludwigshafen, Germany) which has severe side effects, causing inter alia allergic reactions that in one case even were reported to have led to the death of a patient. More severely, certain tumor types are known to be refractory against treatment with Taxol®.

Taxol® treatment is associated with a number of significant side effects and some major classes of solid tumors, namely colon and prostate, are poorly responsive to this compound (see Rowinsky E.K., loc. cit.).

The epothilones A and B are a new class of microtubule stabilizing cytotoxic agents (see Gerth, K. et al., *J. Antibiot.* **49**, 560-3 (1966); Hoefle et al., DE 41 38 042) of the formulae:



wherein Z is hydrogen (epothilone A) or methyl (epothilone B).

These compounds have the following advantages:

(i) they show better water solubility than Taxol and are thus more appropriate for formulation; and

(ii) they have been reported to be active also against the proliferation of cells that, due to the activity of the P-glycoprotein efflux pump which renders them multidrug resistant, show resistance to the treatment with other chemotherapeutics, e.g. Taxol (see Bollag, D. M., et al., "Epothilones, a new class of microtubule-stabilizing agents with a Taxol-like mechanism of action", *Cancer Research* 55, 2325-33 (1995); and Bollag D.M., *Exp. Opin. Invest. Drugs* 6, 867-73 (1997); and

(iii) despite apparently sharing the same, or at least a largely overlapping binding site on the microtubule, the epothilones have been shown to be active against a Taxol<sup>®</sup>-resistant ovarian carcinoma cell line with an altered  $\beta$ -tubulin (see Kowalski, R. J., et al., *J. Biol. Chem.* 272(4), 2534-2541 (1997)).

Due to their impressive biological profile, multiple initial efforts towards the synthesis of epothilones appeared almost simultaneously in the literature. Three groups described total syntheses of epothilone A, and two total syntheses of epothilone B appeared concurrently as well. In addition, a flood of papers appeared which presented partial solutions towards the synthesis of epothilones. Since these studies, many derivatives have been synthesized and their biological profiles have been tested.

Especially epothilone B provides important biological properties that are exemplary for other epothilones:

Epothilone B is appropriate preferably in the treatment of proliferative diseases, such as of gastrointestinal tumors, more preferably (1) a tumor of the colon and/or the rectum (colorectal tumor), especially if it is refractory to a (meaning at least one) representative of the taxane class of anti-cancer agents, in particular paclitaxel, and/or at least one standard treatment with an other chemotherapeutic, especially 5-fluorouracil; (2) a tumor of the genitourinary tract, more preferably a tumor of the prostate, including primary and metastatic tumors, especially if refractory to hormone treatment ("hormone refractory prostate cancer") and/ or treatment with other standard chemotherapeutics; (3) an epidermoid tumor, more preferably an epidermoid head and neck tumor, most preferably a

mouth tumor; (4) a lung tumor, more preferably a non-small cell lung tumor, especially any of these tumors that is refractory to treatment with one or more other chemotherapeutics (especially due to multidrug resistance), especially to treatment with a member of the taxane class of anti-cancer agents, in particular TAXOL®; or (5) a breast tumor, more preferably one that is multidrug resistant, especially refractory to treatment with a member of the taxane class of anti-cancer agents, in particular TAXOL®; relating especially also to the treatment of a multidrug resistant lung tumor (preferably a non-small cell lung tumor), a multidrug resistant breast tumor, or a multidrug resistant epidermoid tumor, or in a broader sense of the invention to a treatment schedule for the treatment of an aforementioned or (in a broader sense of the invention) any other tumor.

Epothilone B is preferably used weekly or three-weekly; preferably for weekly treatment the dose is between about 0.1 and about 6, preferably about 0.1 and about 5 mg/m<sup>2</sup>, more preferably about 0.1 and about 3 mg/m<sup>2</sup>, even more preferably 0.1 and 1.7 mg/m<sup>2</sup>, most preferably about 0.3 and about 1 mg/m<sup>2</sup>; for three-weekly treatment (treatment every three weeks or every third week) the dose is between about 0.3 and about 18 mg/m<sup>2</sup>, preferably about 0.3 and about 15 mg/m<sup>2</sup>, more preferably about 0.3 and about 12 mg/m<sup>2</sup>, even more preferably about 0.3 and about 7.5 mg/m<sup>2</sup>, still more preferably about 0.3 and about 5 mg/m<sup>2</sup>, most preferably about 1.0 and about 3.0 mg/m<sup>2</sup>. This dose is preferably administered to the human by intravenous (i.v.) administration during 2 to 180 min, preferably 2 to 120 min, more preferably during about 5 to about 30 min, most preferably during about 10 to about 30 min, e.g. during about 30 min.

Preferably, especially in the case of weekly treatment, rest periods of more than one week, more preferably of two to ten weeks, more preferably three to six weeks after the preceding treatment may be necessary after for example 3, 4, 6, 8, or more treatment cycles, depending on patient condition, to allow for sufficient recovery from the preceding treatment.

The pharmaceutical compositions comprise from about 0.00002 to about 95%, especially (e.g. in the case of infusion dilutions that are ready for use) of 0.0001 to 0.02%, or (for example in case of infusion concentrates) from about 0.1% to about 95%, preferably from about 20% to about 90%, active ingredient (weight by weight, in each case). Pharmaceutical compositions according to the invention may be, for example, in unit dose form, such as in the form of ampoules, vials, suppositories, dragées, tablets or capsules.

Preferred is an infusion formulation comprising epothilone B and a pharmaceutically acceptable organic solvent. The pharmaceutically acceptable organic solvent used in a formulation according to the invention may be chosen from any such organic solvent known in the art. Preferably the solvent is selected from alcohol, e.g. absolute ethanol or ethanol/water mixtures, more preferably 70% ethanol, polyethylene glycol 300, polyethylene glycol 400, polypropylene glycol or N-methylpyrrolidone, most preferably polypropylene glycol or 70% ethanol or especially polyethylene glycol 300.

Epothilone B may preferably be present in the formulation in a concentration of about 0.1 to about 100 mg/ml, more preferably about 1 to about 100 mg/ml, still more preferably about 1 to about 10 mg/ml (especially in infusion concentrates).

It is a goal of the present invention to provide novel routes to manufacture an intermediate for the synthesis of epothilone B and its predecessor, desoxyepothilone B.

In contrast to a published synthesis by Nicolaou et al. (see J. Am. Chem. Soc. 119, 7974-91 (1997)) for the synthesis of epothilone B, the new route is more convergent, that is, it is based on three rather than two key fragments that have to be assembled to the final product. The disadvantage of the prior art two-fragment strategy consists in the fact that many more steps are required to prepare the individual fragment. Therefore the new synthesis offers large advantages.

#### Detailed Description of the invention

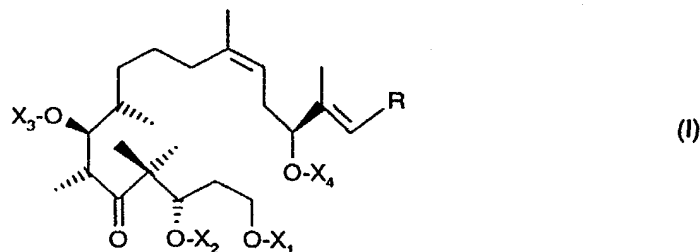
The invention relates to a formal total synthesis route via an intermediate appropriate for the synthesis of epothilone B and analogues thereof. The approach uses macrolactonization for the final ring closure and provides an especially convergent strategy to obtain the key building blocks.

The invention also especially relates to the synthesis of the aldehyde 17 and the aldehyde 18 (see reaction scheme 2) starting from (+)-malic acid, which is largely unrelated to published synthesis of these compounds and is much more practical.

The invention also especially relates to new processes of manufacture for ethyl ketone 30, either via the ester 26 (scheme 4) or acyl sultam 31. The latter compound has been described in the literature (see Synlett (1997), 623). However, if the procedure recommended in that publication is followed, the wrong (namely the 3R-) enantiomer is obtained instead of the desired isomer 31, which is required for the synthesis of epothilones.

The invention also especially relates to the synthesis of 19 via a Pd-catalyzed coupling reaction, which offers the large advantage of highly selective formation of a cis-bond at the double bond connecting carbon atoms 12 and 13 in epothilone B as well as to the new intermediate 19. This compound has not been described previously as a homogenous double bond isomer at the C12-C13 double bond of epothilone B. Surprisingly, the above reaction is stereoselective only for the methyl substituent Z found in the formula of epothilone B given in the introduction.

The invention relates especially to a new method for the synthesis of an intermediate of the formula I



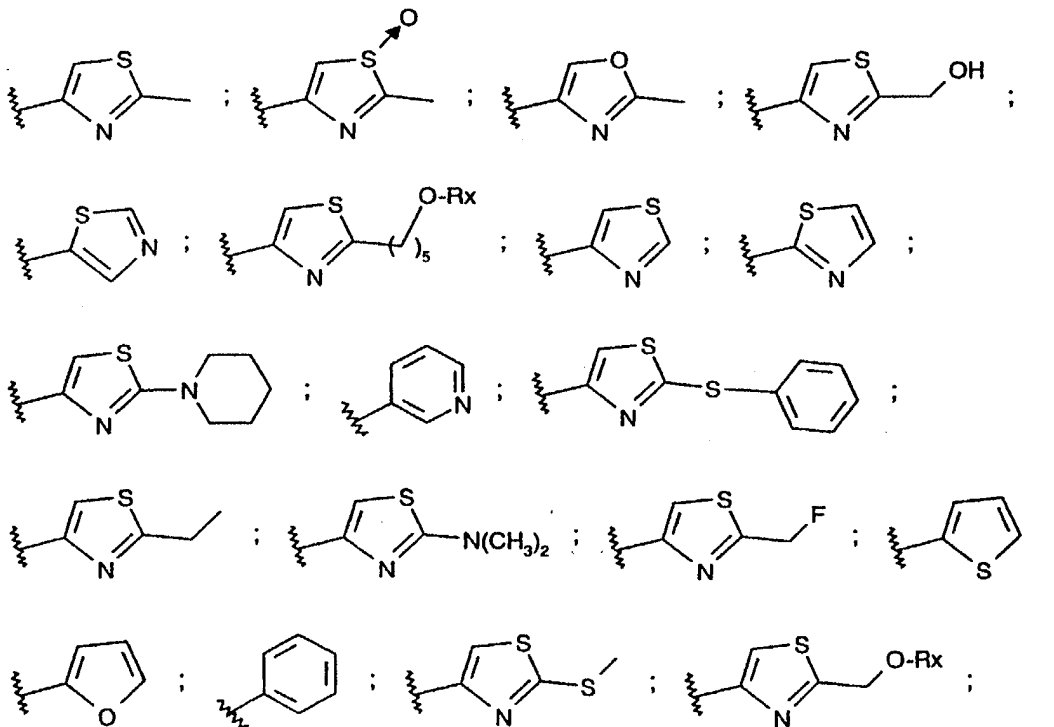
wherein R is a heterocyclyl moiety and X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> are, independently of each other, protecting groups.

The intermediate of the formula I can then be used for the synthesis of epothilone B and analogues thereof via various steps including macrolactonization and epoxidation, using methods known in the art, see especially Nicolaou et al., J. Am. Chem. Soc. 119, 7974-91 (1997). If the epoxidation step is omitted (and, if present, protecting groups are cleaved of), desoxyepothilone B, the analogue of epothilone B where instead of the oxirane ring a double bond is present, can be synthesized.

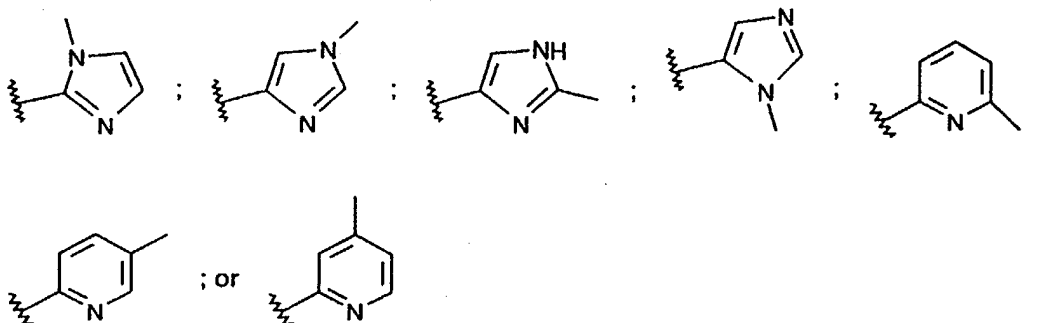
Within the present disclosure, the general definitions used hereinbefore and hereinafter preferably have the following meaning, if not indicated otherwise:

A heterocyclyl moiety R is preferably a monocyclic moiety with 5 or 6 ring atoms, wherein 1 to 3, especially one or two, ring carbon atoms each are replaced by a heteroatom selected from nitrogen, oxygen or sulfur; the heterocyclic moiety may be unsubstituted or substituted by one or more substituents that are preferably independently selected from the group consisting of oxo, lower alkyl, especially methyl, hydroxy-lower alkyl, especially hydroxymethyl, lower alkylmercapto, especially methylmercapto, phenylmercapto, amino, mono- or di-lower alkylamino, especially dimethylamino, halogen-lower alkyl, such as fluoromethyl, or acyloxy-lower alkyl, such as lower alkanoyloxy-lower alkyl, e.g. 5-acetyloxy-pentyl or acetyloxymethyl.

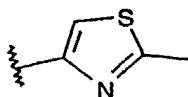
Most preferably, the heterocyclyl moiety has any one of the following formulae:







wherein Rx is acyl, especially lower alkanoyl, such as acetyl;

Most preferably, the moiety R has the formula .

A protecting group is especially selected from the group comprising a silyl protecting group, especially diaryl-lower alkyl-silyl, such as diphenyl-*tert*-butylsilyl, or more preferably tri-lower alkylsilyl, such as *tert*-butyldimethylsilyl or trimethylsilyl; lower alkanoyl, such as acetyl; benzoyl; lower alkoxy carbonyl, such as *tert*-butoxycarbonyl; tetrahydropyranyl; phenyl-lower alkoxy carbonyl, such as benzyloxycarbonyl; and unsubstituted or substituted 1-phenyl-lower alkyl, such as benzyl or *p*-methoxybenzyl.

The protecting groups may be present in any precursors and intermediates and should protect the functional groups concerned against unwanted secondary reactions, such as acylations, etherifications, esterifications, oxidations, solvolysis, and similar reactions. In certain cases, the protecting groups may, in addition to this protection, effect a selective, typically stereoselective, course of reactions. It is a characteristic of protecting groups that they lend themselves readily, i.e. without undesired secondary reactions, to removal, typically by solvolysis, reduction, photolysis or also by enzyme activity, for example under conditions analogous to physiological conditions, and that they are not present in the end-products. The specialist knows, or can easily establish, which protecting groups are suitable with the reactions mentioned hereinabove and hereinafter.

The protection of functional groups by such protecting groups, the protecting groups themselves, and their cleavage reactions are described for example in standard reference works,

such as J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene, "Protective Groups in Organic Synthesis", Wiley, New York 1981, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981, in "Methoden der organischen Chemie" (*Methods of organic chemistry*), Houben Weyl, 4th edition, Volume 15/I, Georg Thieme Verlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosäuren, Peptide, Proteine" (*Amino acids, peptides, proteins*), Verlag Chemie, Weinheim, Deerfield Beach, and Basel 1982, and in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate" (*Chemistry of carbohydrates: monosaccharides and derivatives*), Georg Thieme Verlag, Stuttgart 1974.

The prefix "lower" means that the respective moiety preferably has up to and including a maximum of 7 carbon atoms, more preferably up to 4 carbon atoms.

Lower alkyl can be linear or branched and is especially methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl.

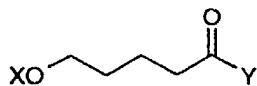
Halogen is preferably fluorine, chlorine, bromine or iodine.

Any reference to other documents or publications within this application means that the respective document or publication is included by reference into the present disclosure.

The process steps making up the process of the invention and the preferred aspects thereof can be described preferably as follows:

Hereinbefore and hereinafter, the definitions of the moieties R, X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> have the meaning given under formula I, if not indicated otherwise. A moiety X, where mentioned, stands for a protecting group as defined above (and may, depending on the exact position, correspond to any of X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> if appropriate).

The reaction sequence starts with a compound of the formula II

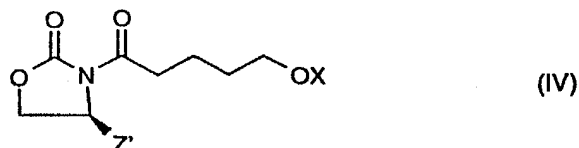


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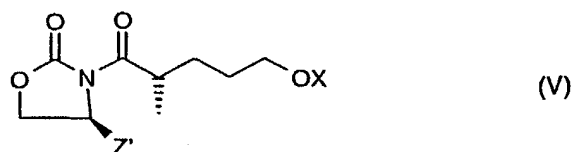
wherein Y is the radical of an organic or inorganic acid devoid of its dissociable hydrogen, e.g. halogen, especially chlorine, and X is a protecting group as described above, especially benzyl; which is reacted with an oxazolidone of the formula III



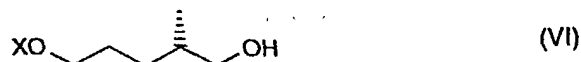
wherein Z' is lower alkyl, e.g. isopropyl, or preferably phenyl-lower alkyl, especially benzyl, in an appropriate solvent, e.g. tetrahydrofuran, in the presence of a strong base, especially methyl magnesium bromide, and then of an appropriate tertiary amino base, such as 4-dimethylaminopyridine; or preferably of an alkali metal alkylid, such as n-butyl-lithium; at low temperatures, e.g. in the range from -80 to + 10 °C, yielding a compound of the formula IV,



wherein X and Z' have the meanings given above; (IV) is then C-methylated, e.g. with a halomethane, especially methyl iodide, in the presence of a strong base, e.g. sodium hexamethyldisilazide, to yield a compound of the formula V,



wherein X and Z' are defined as above; from that compound, then a compound of the formula VI,

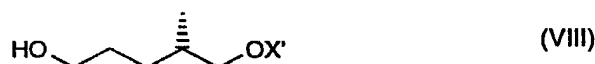


wherein X is as given above is set free by reductive cleavage, e.g. by reaction with a complex hydride, such as lithium aluminium hydride; then, a protecting group X' selected from the protecting groups mentioned above for X<sub>1</sub> to X<sub>4</sub>, but different from X in formula VI, preferably tert-butyl-dimethylsilyl, is introduced at the free hydroxy group that allows that the protecting group X in the compound of formula VI can be cleaved off without affecting the

newly introduced protecting group, e.g. by reaction with an alkylsilylhalogenide, such as tert-butyldimethylsilyl chloride, to yield a bis-protected compound of the formula VII,



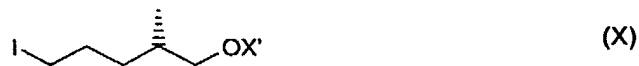
with X and X' as described above; from this compound, then the protecting group X, preferably benzyl, is cleaved off under appropriate conditions, e.g. by catalytic transfer hydrogenolysis, reaction with lithium 4,4'-di-tert-butyl-biphenyl or by catalytic hydrogenation, to yield a compound of the formula VIII,



with X' as defined for the compound of the formula VII; that compound VIII is then reacted with a halogenide of an organic sulfonic acid to yield the corresponding sulfonic acid ester of the formula IX,



wherein Q is organic sulfonyl, especially alkanesulfonyl, such as methanesulfonyl, and that sulfonyl ester is then reacted with a metal iodide, especially sodium iodide, to yield the corresponding iodide compound of the formula X,



with X' as defined above.

This is the synthesis of one of the three intermediates for the convergent synthesis.

Independently from that sequence of reactions,

a) a compound of the formula XI,



wherein R is as described under formula I and Hal is halogen, especially chlorine, is reacted with a tri-alkyl phosphite, especially triethyl phosphite, to yield a phosphonate compound of the formula XII,



wherein R is as defined under formula I and each of A is alkyl, especially ethyl.

Independently, (5S)-(2,2-cyclohexylidene)-4-oxo-1,3-dioxolane (synthesized starting from L-(-)-malic acid, see Hanessian et al., J. Orgn. Chem. **58**, 7768-81 (1993)) is reacted with  $\text{BH}_3\text{-Me}_2\text{S}$  complex = **dimethylsulfide  $\text{BH}_3 \times \text{Me}_2\text{S}$  ist verzichtbar** to yield 3(S)-dihydro-3-hydroxy-2(3H)-furanone (compound **11** in reaction scheme 2 below); that is then protected by introduction of a protecting group  $\text{X}_4$ , especially using a lower alkylsilyl halogenide, such as tert-butyldimethylsilylchloride, to yield a compound of the formula XIII,



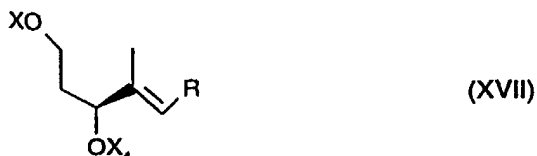
wherein  $\text{X}_4$  is a protecting group, especially tert-butyldimethylsilyl; the compound of formula XIII is then reacted with an methyl metal or methyl metal derivative, especially methyl lithium, to the novel compound of the formula XIV,



wherein  $\text{X}_4$  is as defined under formula XIII; the compound of formula XIV is reacted with a further reagent capable of introducing a protecting group, especially an alkylsilyl halogenide, such as tert-butyldimethylsilyl chloride, yielding a compound of the formula XV,



wherein X and  $\text{X}_4$  are a protecting group, especially tert-butyldimethylsilyl, which compound is then reacted with a phosphonate compound of the formula XII given above in the presence of a strong base, especially n-butyl lithium, yielding a compound of the formula XVII,



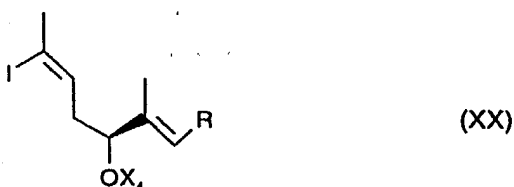
wherein X and X<sub>4</sub> are as defined under formula XIII and R is as defined under formula I; the compound of the formula XVII is then deprotected partially under appropriate conditions (e.g., if X is tert-butyldimethylsilyl, by using aqueous hydrofluoric acid) to give a compound of the formula XVIII,



wherein the moieties X<sub>4</sub> and R are as defined under formula XVII; the compound of the formula XVIII is oxidized selectively, e.g. using dimethylsulfoxide and oxalylchloride in dichloromethane, to the corresponding aldehyde of the formula XIX,



wherein R and X<sub>4</sub> are as defined under formula XVII, which is then, by reaction with a strong base, especially n-butyl lithium, and iodine in the presence of triphenylphosphonium iodide (either with isolation of the iodoethyl phosphonium iodide or in a one pot synthesis), and subsequent addition of a different or the same base as above, especially sodium hexamethyldisilazide, converted into a compound of the formula XX,



(this reaction being highly specific in yielding mainly or purely the cis-compound wherein R and X<sub>4</sub> are as defined under formula XVII.

This reaction sequence is allowing for the introduction of a large variety of heterocyclic moieties R and thus providing an important new way of synthesizing analogs of epothilone B and desoxyepothilone B wherein R has one of the other meanings than 2-methylthiazolyl given above under formula (I)

The sequence of reactions from XIII to XV, especially the reaction from XIII to XIV and the reaction from XIV to XV, as well as the whole sequence leading from L-malic acid to XX (as described in the examples), are new and form a special part of the invention.

The compounds of the formulae XIV (especially compound 13 in scheme 2), XVII (if R is other than 2-methylthiazol-4-yl and X<sub>4</sub> is other than tert-butyldimethylsilyl) (especially 15 in scheme 2), XVIII (if R is other than 2-methylthiazol-4-yl and X<sub>4</sub> is other than tert-butyldimethylsilyl) (especially 16 in scheme 2), the compound of formula XX if R is other than 2-methylthiazol-4-yl, and compound 18 in scheme 2, are new and are also part of the invention.

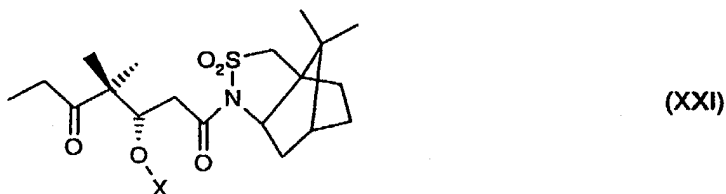
The compound of the formula XX is the second of the three intermediates for the convergent synthesis.

The third intermediate for the convergent synthesis is manufactured preferably by one of the two ways (a) and (b) described hereinafter:

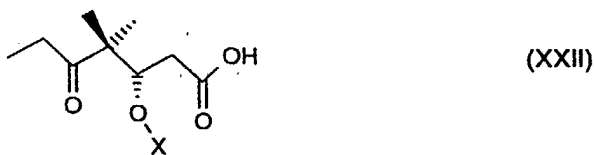
(a) (see also scheme 4) Diethylketon is reacted in the presence of zinc dust (activated, e.g. with 1,2-dibromoethane) in the presence of B(OCH<sub>3</sub>)<sub>3</sub> with ethyl 2-bromo-2-methylpropanoate (Fluka, Buchs, Schweiz) to ethyl 2,2-dimethyl-3-ethyl-3-hydroxypentanoate 22, which is then reacted with a dehydrating agent, especially phosphorus pentoxide, to ethyl (E)-2,2-dimethyl-2-ethyl-3-pentenoate 23; which is then reacted in the presence of an appropriate complex hydride, e.g. lithium aluminium hydride, to E-2,2-dimethyl-3-ethyl-3-penten-1-ol 24; this is then oxidised with an appropriate oxidant, e.g. dimethylsulfoxide in dichloromethane and oxalyl chloride, to (E)-2,2-dimethyl-3-ethyl-3-pentenal 25, which is then reacted with (S)-(-)-2-hydroxy-1,2,2-triphenyl acetate (FLUKA) in the presence of a strong base, e.g. Li-diisopropylamide, to (1S)-2,2,1-triphenyl-2-hydroxyethyl-(3S,E)-4,4-dimethyl-5-ethyl-3-hydroxy-5-heptenoate 26; that compound is transformed, by reaction with an appropriate complex hydride, e.g. lithium aluminium hydride, into (S)-(E)-4,4-dimethyl-5-ethyl-5-heptene-1,3-diol

**28**, which is then converted, by reaction with acetone in the presence of anhydrous copper sulfate, a strong organic acid, e.g. p-toluene sulfonic acid, and a tertiary nitrogen base, e.g. pyridine, to give (S)-(E)-2,2-dimethyl-[1,3]dioxan-4-yl)-3-ethyl-2-methyl-pent-3-ene **29**; this compound is then converted to the third intermediate for the convergent synthesis, the ethyl ketone (S)-2-(2,2-dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one **30** by ozonolysis.

(b) (see scheme 3) Alternatively, **30** can be obtained advantageously by reaction of (2R)-N-acetylbornane-10,2-sultam (see Tetrahedron Lett. **33**, 2439 (1992)) in the presence of a dialkylborane triflate or dialkylborane chloride, especially diethylborane triflate (which can, but does not have to be, generated in situ from triethylborane and  $\text{CF}_3\text{SO}_3\text{H}$ ) and after addition of a tertiary nitrogen base, e.g. diisopropylethyl amine, with 2,2-dimethyl-3-oxo-pentanal (see J. Am. Chem. Soc. **119**, 7974 (1997)) that leads to the sultam product **31**, which is then reacted, in the presence of a tertiary nitrogen base, such as 2,6-lutidine, with a reagent appropriate for the introduction of a protecting group, e.g. an alkylsilylhalogenide, especially tert-butyldimethylsilyl-triflate, to give a compound of the formula XXI

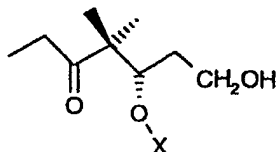


wherein X is a protecting group, especially tert-butyldimethylsilyl (especially compound **32**); the compound of formula XXI is then converted into the corresponding free acid of the formula XXII by reaction with an appropriate aqueous base, e.g. LiOH, NaOH, KOH, or LiOOH, especially with LiOOH



wherein X is as defined under formula XXI (especially compound **33**); the compound of formula XXII is then reduced to the corresponding alcohol of the formula XXIII



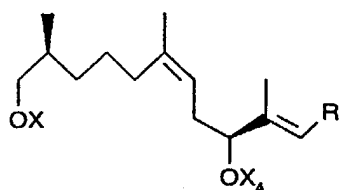


(XXIII)

wherein X is as defined under formula XXI (especially compound 34), by reaction eg. with Borane/dimethylsulfide, and finally that compound is deprotected and transformed into compound 30 by reaction in acetone/acid, such as acetone/trifluoroacetic acid.

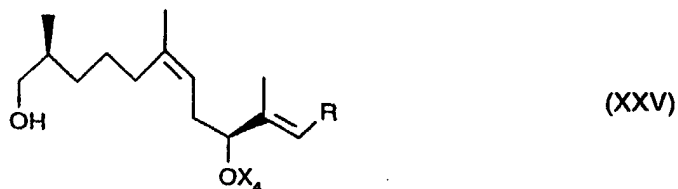
Thus, the third intermediate for the convergent synthesis of the compound of the formula I is prepared.

In a next step, first the two intermediates of the formulae X and XX (preferably compounds 8 and 18 in scheme 5) are coupled by reaction of the compound of the formula X with a suspension of powdered Zn/Cu couple in the presence of an activator, e.g. 1,2-dibromoethane, in the presence of halotrialkylsilane, such as chlorotrimethylsilane (if necessary with addition of trifluoromethanesulfonate and catalytic amounts of mercury(II) acetate to complete the first part of the reaction, and then addition of XX and a Pd(0)-complex yielding a compound of the formula XXIV,



(XXIV)

wherein X and X<sub>4</sub> each are a protecting group, especially tert-butyldimethylsilyl, and R is as defined under formula I; the advantage of this coupling is that it yields the cis-isomer of the compound of the formula XXIV in high yield and stereospecificity the compound of the formula XIV is then selectively deprotected, e.g. (in the case of X = alkylsilyl, especially tert-butyl-dimethylsilyl) by campher sulfonic acid, to give a compound of the formula XXV,



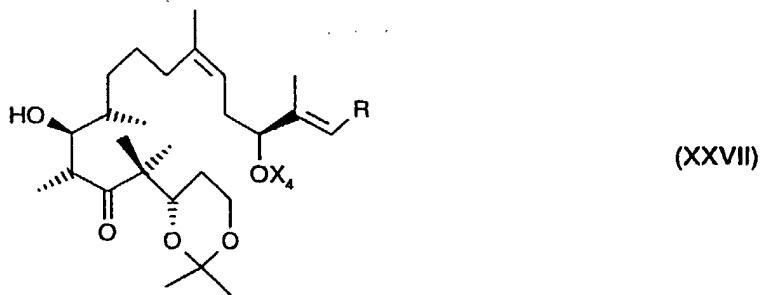
wherein  $X_4$  and R are as defined under formula XXIV; the compound of the formula XXV is then oxidized with an appropriate oxidant, e.g. Dess-Martin periodinane, to the corresponding aldehyde of the formula XXVI



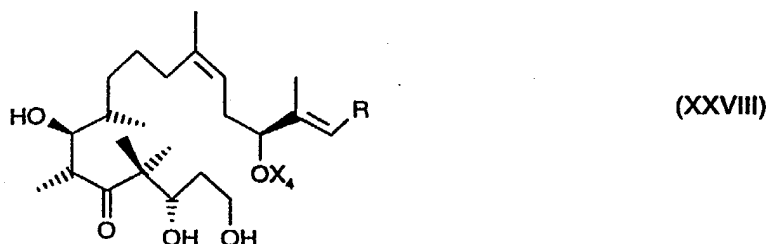
wherein  $X_4$  and R are as defined under formula XXIV.

The compounds of the formulae XXIV and XXV in essentially isomeric pure *cis*-form, especially if R is other than 2-methylthiazolyl) are new and also part of the invention, as well as the coupling reaction of the compounds of the formulae X and XX to the compound of the formula XXIV.

The third intermediate of the convergent synthesis, compound 30, is then reacted with the compound of the formula XXVI (preferably compound 21) in an Aldol reaction, preferably by reaction in the presence of lithium diisopropylamide (LDA) that is first reacted with compound 30, followed by addition of the compound of the formula XXVI, resulting in a compound of the formula XXVII,



wherein  $X_4$  and R are as defined under formula I; the compound of the formula XXVII is then deprotected under removal of the acetal moiety, e.g. using pyridinium-p-toluenesulfonate, yielding a compound of the formula XXVIII,



wherein  $X_4$  and R are as defined under formula I; finally, the compound of the formula I is obtained by introduction of protecting groups  $X_1$ ,  $X_2$  and  $X_3$  with appropriate reagents, e.g. alkylsilyl halogenides or alkylsilyl trifluoromethanesulfonates, especially tert-butyl-dimethylsilyltrifluoromethanesulfonate, in the presence of an appropriate tertiary nitrogen base, such as 2,6-lutidine.

The compound of the formula XXIV, especially where R is other than 2-methylthiazol-4-yl, is also part of the invention.

All reactions are done in appropriate solvents, at appropriate temperatures and, if necessary, under an inert gas, such as argon or nitrogen.

The invention relates also to any novel intermediates and to any novel ways of synthesis of such intermediates, as well as to novel single reaction steps, especially those leading to such novel intermediates, and combinations of such reaction steps.

The skilled person will understand that the reaction conditions given above can be replaced by analogous reaction conditions that are in principle known in the art. In addition, the skilled person will be able to select the appropriate specific reaction conditions for the reaction steps given hereinbelow and hereinafter where reactions are described generally herein. All those reaction conditions are included in the scope of the present invention.

The reactions given above are preferably carried out under conditions analogous to those given in the Examples.

The invention relates most especially to the above reaction sequences where the respective intermediates and educts mentioned in the examples are used instead of the general formulae II to presented above.

The starting materials are known, can be synthesized according to known procedures, are available commercially or can be synthesized in analogy to the materials given below in the examples.

#### Examples

The following examples are intended to illustrate the invention without being intended to mean any restriction of the scope of the invention:

Temperatures are given in degrees Celsius (°C). The abbreviations used have the following meanings:

h	hour(s)
min	minute(s)
m.p.	melting point
MW	molecular weight
MS	Mass Spectroscopy
NaHMDS	sodium hexamethyldisilazide
NMR	Nuclear Magnetic Resonance
OTBDMS	tert-butyl-dimethylsilyloxy
Pd(PPh <sub>3</sub> ) <sub>4</sub>	Palladium-tetrakis-(triphenylphosphin)
PPTS	pyridinium-p-toluenesulfonate
r.t.	room temperature
TBDMSO	tert-butyl-dimethylsilyloxy
THF	tetrahydrofurane
tlc	thin layer chromatography (Polygram SIL G/UV, Macherey & Nagel, Düren, FRG)

Where physical data are not provided, the respective compound is used directly in the subsequent reaction step.

Flash chromatography is performed on silica gel columns (Kieselgel 60 (0.035-0.07 mm), Fluka, Buchs, Schweiz)

**1) "C5" fragment (Scheme 1)**

**a) 5-Benzoyloxypentanoyl Chloride 1**

Oxalyl chloride (1.49 ml, 17.06 mmol, 1.5 equiv) is added dropwise under nitrogen atmosphere to a solution of 2,368 g (11.37 mmol) 5-benzoyloxypentanoic acid [L. Börjesson et al., J. Org. Chem. 60, 2989 - 2999 (1995)] in 15 ml of CH<sub>2</sub>Cl<sub>2</sub>. The mixture is stirred for 90 min at r. t. and 15 min at 40 °C. Removal of the solvent *in vacuo* gives 2.425 g (94%) of 5-benzoyloxypentanoyl chloride 1 as a colourless oil. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 171.3; 137.4; 128.7; 128.5; 128.3; 69.4; 46.2; 29.8; 22.3; 19.1

**b) (S)-3-(5-Benzoyloxy-1-oxopentyl)-4-(methylethyl)-2-oxazolidinone 2a (Z = isopropyl in Scheme 1)**

9,6 ml (28.8 mmol, 1.2 eq) of a solution of methyl magnesium bromide (3.0 M in THF) are added dropwise to a solution of (S)-4-methylethyl-2-oxazolidinone (3.100 g, 24.0 mmol) in THF (60 ml) at 0 °C within 15 min. The mixture is stirred for 15 min at 0 °C. 4-Dimethylaminopyridine (59 mg, 0.48 mmol, 0.02 equiv) is added and the mixture is cooled to -78 °C. A solution of 5-benzoyloxypentanoyl chloride 1 (6,625 g, 29.22 mmol, 1.22 eq) in THF (20 ml) is added slowly within 30 min. The mixture is stirred for 15 min at -78 °C and then for 30 min at 0 °C. Saturated aqueous NH<sub>4</sub>Cl solution (40 ml) is added with stirring. The organic phase is separated and the aqueous layer is extracted with diethyl ether (3 x 100 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 2:1) affords (S)-3-(5-benzoyloxy-1-oxopentyl)-4-(methylethyl)-2-oxazolidinone 2 (5.602 g, 73%) as a colourless oil which crystallizes upon standing in the cold. Recrystallization from pentane / diethyl ether yields colourless crystals, m. p. 133 °C. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 173.0; 154.0; 138.5; 128.3; 127.6; 127.4; 72.8; 69.9; 63.3; 58.3; 35.2; 29.0; 28.3; 21.1; 17.9; 14.6

**c) 3-(5-Benzoyloxy-2S-methyl-1-oxopentyl)-4S-(methylethyl)-2-oxazolidinone 3a (Z = isopropyl in Scheme 1)**

To 10.1 ml (10.1 mmol, 1.1 equiv) of a solution of sodium hexamethyldisilazide (NaHMDS, 1.0 M in THF) is added a solution of (S)-3-(5-benzyloxy-1-oxopentyl)-4-(methylethyl)-2-oxazolidinone **2** (2,928 g, 9.17 mmol) in 10 ml of THF dropwise at -78 °C. The mixture is stirred for 1 h at -78 °C. A solution of iodomethane (2.9 ml) in 12.0 ml of THF is added dropwise. The mixture is stirred for 8 h at -78 °C. Saturated aqueous NH<sub>4</sub>Cl solution (40 ml) is added with stirring. The organic phase is separated and the aqueous layer is extracted with diethyl ether (3 x 100 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue (ratio of the diastereomeric alkylation products about 10:1) by flash column chromatography (pentane / diethyl ether 2:1) affords 3-(5-benzyloxy-2S-methyl-1-oxopentyl)-4S-(methylethyl)-2-oxazolidinone **3** (2.142 g, 70%) as a colourless oil (3 : 1 mixture of **3a** and its 2R diastereomer). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 176.9; 153.6; 138.5; 128.3; 127.5; 127.4; 72.8; 70.2; 63.1; 58.4; 37.5; 29.7; 28.4; 27.4; 18.0; 17.9; 14.6

d) (S)-5-Benzyloxy-2-methyl-pentan-1-ol **4**

Lithium aluminium hydride (235 mg, 6.19 mmol, 1.0 equiv) is added portionwise within 45 min at 0 °C to a solution of 2.064 g (6.19 mmol) of 3-(5-benzyloxy-2S-methyl-1-oxopentyl)-4S-(methylethyl)-2-oxazolidinone **3** in 35 ml of absolute diethyl ether. The mixture is stirred at 0 °C for 15 min and analyzed by tlc. If starting material can still be detected, lithium aluminium hydride addition is continued until completion of the reaction. 235 µl of water, 235 µl of aqueous sodium hydroxide solution (15%) and 610 µl of water are subsequently added to the reaction mixture (or the volumes corresponding to the amount of lithium aluminium hydride added, respectively). The mixture is stirred until the precipitation of a white solid is complete and filtered through a small plug of celite. The filtrate is concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 1:1) affords (S)-5-benzyloxy-2-methyl-pentan-1-ol **4** (1.160 g, 90%) as a colourless oil. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 138.5; 128.3; 127.6; 127.5; 72.9; 70.6; 68.1; 35.5; 29.5; 27.1; 16.5

[Alternatively (using Z = benzyl in reaction scheme 1), **4** can be synthesized as follows:

b\*) 4(S)-(Benzyl)-3-(5-benzyloxy-1-oxopentyl)-2-oxazolidinone **2a** (Z = isopropyl in Scheme 1)

To a solution of 2.03 g of 4-(S)-benzyl-oxazolidin-2-one in 30 ml of THF, 7.23 ml of a 1.6 M solution of n-BuLi in hexane at -78° are added over a period of 10 min. To this solution then 2.86 g of 5-benzyloxypentanoyl chloride **1** are added at the same temperature and the mixture is stirred at -78° for 30 min. After that time the reaction is quenched by the addition of 10 ml of saturated aqueous NH<sub>4</sub>Cl, the THF is removed by evaporation, the residue is diluted with dichloromethane/water and the organic layer is separated off. The aqueous solution is extracted three times with 30 ml of dichloromethane, respectively, and the combined organic extracts are washed with 50 ml of 1N NaOH (once) and 50 ml of brine (once). After drying over MgSO<sub>4</sub> and evaporation of solvent the residue is purified by FC in hexane/ether 1/1 to give 3.76 g of **2b** as an oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 7.35 - 7.15 m (10H); 4.65 m (1H); 4.5 s (2H); 4.15 d (2H); 3.5 t (2H); 3.25 dd (1H); 3.25 dd (1H); 2.95 m (2H); 2.7 dd (1H); 1.90 - 1.45 m (4H).

c\*) 4S-(Benzyl)-3-(5-benzyloxy-2S-methyl-1-oxopentyl)- 2-oxazolidinone **3b** (Z = benzyl in Scheme 1)

All non-aqueous steps are carried out under argon. A solution of 205 g of compound **2b** in 800 ml of THF is added dropwise at -75° to 690 ml of a 1M solution of NaHMDS in THF. After completion of the addition (ca. 2h), the solution is stirred for an additional 30 min at -70° after which time a solution of 198 ml of methyl iodide in 800 ml of THF is added dropwise at the same temperature (ca. 45 min). The mixture is then stirred at -70° for 75 min, the cooling bath is removed and the mixture is allowed to warm to room temperature. After addition of 300 ml of THF/water 1/1 followed by 250 ml of saturated aqueous NH<sub>4</sub>Cl the organic layer is separated and the remaining aqueous solution is extracted three times with 300 ml of t-butyl-methyl ether each. The combined organic extracts are evaporated to dryness and the residue is purified by FC in t-butyl-methyl ether/hexane 1/1 to yield a ca. 11/1 mixture of diastereoisomers. Recrystallization of this material from ethyl acetate/ hexane (ca. 1/10) gave 98.5 g of **3a**, which was diastereomerically pure. M. p. 51.5 - 53.3 °C. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 7.5 - 7.15 m (10H); 4.65 m (1H); 4.45 s (2H); 4.1 m (2H); 3.75 m (1H); 3.45 m (2H); 3.25 dd (1H); 2.75 dd (1H); 1.90 - 1.45 m (4H); 1.20 d (3H).

d\*) (S)-5-Benzoyloxy-2-methyl-pentan-1-ol **4**:

150 ml of a 1M solution of LiAlH<sub>4</sub> in THF at 5° are added over a period of 20 min to a solution of 67.5 g of compound **3b** in 700 ml of dry THF are added. The reaction mixture is stir-

red at room temperature for 1 h and then quenched by addition of 17 ml of THF/water 10/7 followed by 6.5 ml of 4N NaOH and 15 ml of water. The resulting precipitate is removed by filtration, the residue washed with 250 ml of THF and the filtrate is evaporated. The residue is then redissolved in 250 ml of ethyl acetate and this solution extracted with 200 ml each of water, 1N NaOH, water, 1N HCl, and water followed by 300 ml of brine. The solvent is evaporated and the residue is three times co-evaporated with 100 ml of toluene. Vacuum distillation of the residue at 0.69 Torr gave 26 g of **4a** as a colourless oil (b. p. 105°).

MS ( $C_{13}H_{20}O_2$ ; 208.3): 209 [M+H].  $^1H$ -NMR ( $CDCl_3$ ):  $\delta$  = 7.35 - 7.25 m (5H); 4.5 s (2H); 3.45 m (4H); 1.8 - 1.4 m (3H); 1.2 m (1H); 0.95 d (3H).]

Further process after any of the 2 variants for synthesis of compound **4**:

e) (S)-1-Benzyloxy-5-(tert-butyldimethylsilyloxy)-4-methyl-pentane **5**

Imidazole (1.230 g, 18.06 mmol, 2.6 equiv) and *tert*-butyl-dimethylsilyl chloride (1.230 g, 9.03 mmol, 1.3 equiv) are added to a solution of (S)-5-benzyloxy-2-methyl-pentan-1-ol **4** (1.447 g, 6.95 mmol) in dimethyl formamide (5.5 ml). The mixture is stirred for 1 h at 40 °C. Purification of the reaction mixture by flash column chromatography (pentane / diethyl ether 20:1) affords (S)-1-benzyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane **5** (1.985 g, 89%) as a colourless oil (the reaction mixture is poured directly without aqueous workup onto a flash chromatography column which is pre-wetted with the eluent).

$^{13}C$ -NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 138.7; 128.3; 127.5; 127.4; 72.8; 70.8; 68.2; 35.6; 29.6; 27.2; 25.9; 18.3; 16.6; -5.4.

f) (S)-5-(tert-Butyldimethylsilyloxy)-4-methyl-pentan-1-ol **6**

Three variants (i), (ii) or (iii) are possible:

(i) Catalytic Transfer Hydrogenolysis Protocol: 48.5 mg of  $Pd(OH)_2$  on activated charcoal (20%) (Pearlman's catalyst) is added to a solution of (S)-1-benzyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane **5** (485 mg, 1.5 mmol) in 12.0 ml of absolute ethanol and 6.0 ml of cyclohexene. The mixture is heated under reflux until the reaction is completed (tlc monitoring). If starting material can still be detected after 8 h, some catalyst is added and refluxing is continued until the reaction is completed. After cooling to room temperature the catalyst is filtered off. The filtrate is concentrated in vacuo. Purification of the residue by



flash column chromatography (pentane / diethyl ether 5:1) affords (*S*)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentan-1-ol **6** (565 mg, 97%) as a colourless oil.

(ii) Debenzylation with Lithium 4,4'-di-*tert*-butyl-biphenyl (LiDTBBP):

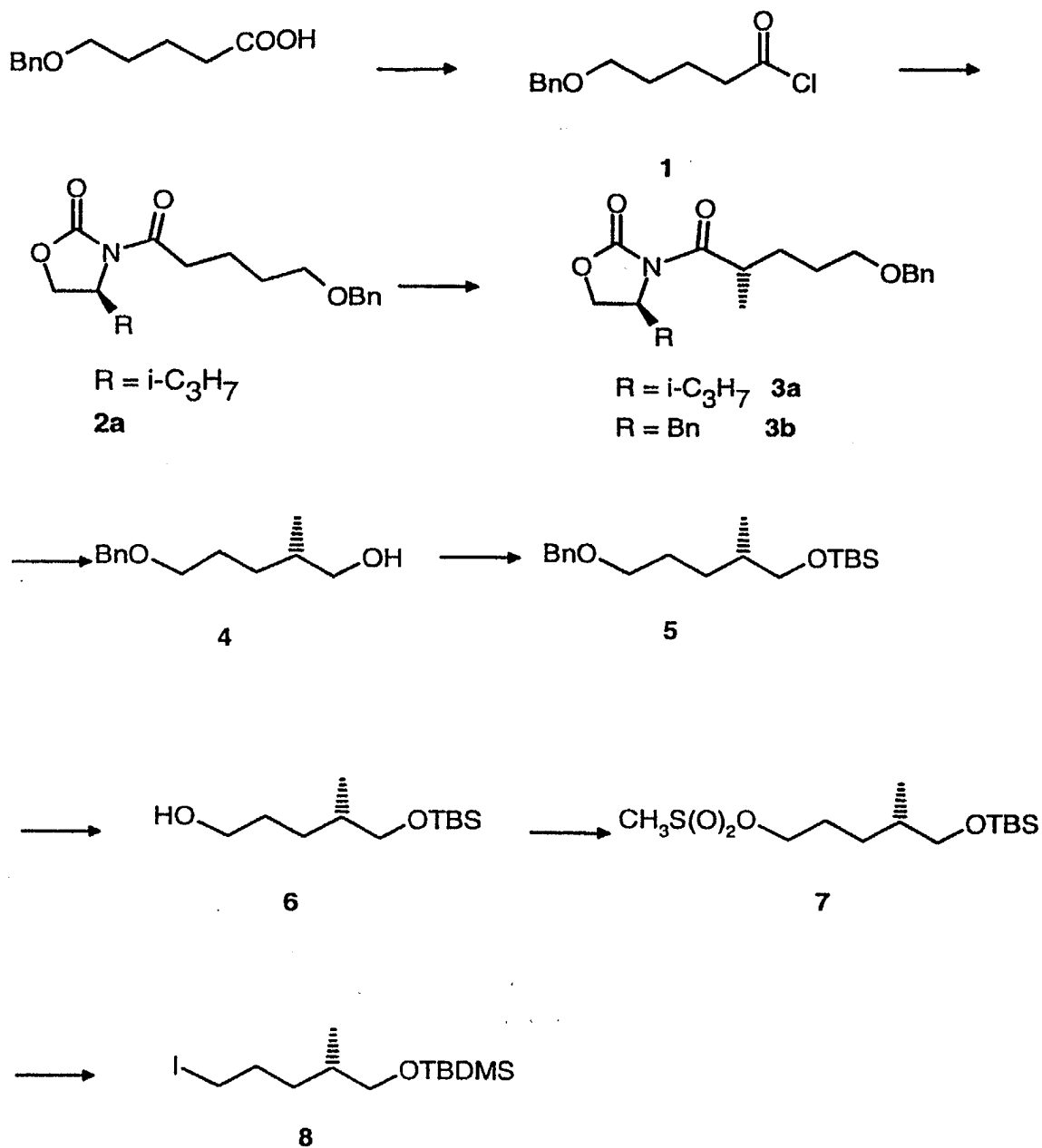
Preparation of LiDTBBP solution: With stirring, 4,4'-di-*tert*-butyl biphenyl (3.6 g) under an Argon atmosphere is added at 0 °C to a suspension of lithium (30% in mineral oil) in THF (30 ml). Stirring is continued for 2 h at r.t. The resulting deep green solution is added dropwise to a solution of (*S*)-1-benzyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane **5** (673 mg, 2.09 mmol) in 10 ml of THF at -78 °C, until the colour of the mixture remains green (or until tlc analysis shows completion of the reaction, respectively). Saturated aqueous NH<sub>4</sub>Cl solution (10 ml) is added with stirring. The organic phase is separated and the aqueous layer is extracted with diethyl ether (3 x 50 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 5:1) affords (*S*)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentan-1-ol **6** (471 mg, 97%) as a colourless oil. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 68.29; 63.36; 35.57; 30.24; 29.25; 25.98; 18.38; 16.77; -5.34

(iii) Catalytic hydrogenation: 102 g of compound **5** in 1800 ml of ethanol/cyclohexane 2/1 are hydrogenated over 10% Pd-C (10g) at room temperature and atmospheric pressure for 16h. After removal of the catalyst by filtration the solvents are evaporated and the residue is purified by silica gel chromatography in hexane/ethyl acetate 6/1 → 1/1 to yield 72 g of **6**.

g) (*S*)-1-Methanesulfonyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane **7**

Triethyl amine (413 µl, 3.09 mmol, 1.53 equiv) and methanesulfonyl chloride (212 µl, 2.73 mmol, 1.35 equiv) is added to a solution of (*S*)-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentan-1-ol **6** (471 mg, 2.03 mmol) in 6.5 ml of dichloromethane. The mixture is stirred for 15 min at 0°C, diluted with diethyl ether (30 ml), washed with water (5 ml), 1.0 M hydrochloric acid (5 ml), saturated aqueous sodium bicarbonate solution (5 ml), and brine (5 ml). The organic phase is separated, dried over magnesium sulfate and concentrated *in vacuo*. (*S*)-1-methanesulfonyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane **7** (472 mg, 99%) is obtained as a colourless oil. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 70.44; 67.98; 37.41; 35.31; 28.99; 26.80; 25.95; 18.34; 16.56; -5.37, -5.38 (-SiMe<sub>2</sub>tBu).

Scheme 1

h) (S)-1-iodo-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane 8

Anhydrous sodium iodide (600 mg, 4.0 mmol, 2 equiv) is added to a solution of (*S*)-1-methanesulfonyloxy-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane **7** (622 mg, 2.0 mmol) in

3.0 ml of absolute acetone. The mixture is stirred for 2 h at 50 °C. 10 ml of a mixture of brine and water (1:1) are added, and the mixture is extracted with diethyl ether (3 x 20 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 20:1) affords (S)-1-iodo-5-(*tert*-butyldimethylsilyloxy)-4-methyl-pentane **8** (647 mg, 94%) as a colourless oil. FG 342.34;  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 68.1, 35.1, 34.3, 31.3, 26.0, 16.7, 7.4, -5.3

## **2) The Thiazole Segment (Scheme 2)**

### **a) 4-Chloromethyl-2-methylthiazole **9****

A solution of thioacetamide (3.757 g; 50 mmol) is added dropwise to a saturated solution of 1,3-dichloroacetone (6.683 g, 50 mmol) in acetone. After a few minutes, a crystalline solid precipitates (the reaction can be initiated or accelerated by immersion of the reaction flask into an ultrasonic bath for a few seconds). In order to complete crystallisation, the reaction flask is left stand over night at r.t. The resulting suspension is filtered through a suction filter. The solid is washed with a few ml of acetone. A solution of the solid in ethanol (40 ml) is refluxed for 3 h. After the mixture is cooled to r.t. the solvent is removed *in vacuo*. Saturated aqueous sodium bicarbonate solution (50 ml) is added, and the mixture is extracted with diethyl ether (3 x 50 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. 4-Chloromethyl-2-methylthiazole **9** (7.138 g, 97%) is obtained as a pale yellow oil after complete evaporation of the solvent.  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$ (ppm) = 7.14 (s, 1H, H-5); 4.65 (s, 2H,  $-\text{CH}_2\text{Cl}$ ); 2.72 (s, 3H,  $-\text{CH}_3$ );  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$ (ppm) = 166.9; 151.6; 116.9; 40.7; 19.1

**CAUTION:** The reaction is strongly exothermic and it may not immediately take place after addition of the thioacetamide is started. The onset of the reaction can be delayed to the point where all of the thioacetamide has already been added, resulting in a vigorous and uncontrolled blow-up of the reaction mixture. It is therefore advisable to add the thioacetamide at 50°. If the reaction is not initiated after addition of 10% of the projected amount of thioacetamide the addition should be halted and only continued after onset of the reaction.

### **b) Diethyl-(2-methylthiazol-4-yl)-methanephosphonate **10****

A mixture of 4-chloromethyl-2-methylthiazole 9 (3.691 g, 25 mmol) and triethyl phosphite (6.64 ml, 50 mmol) is stirred for 6 h at 160 °C. Excess triethyl phosphite is distilled off under oil pump vacuum (4 mm). Purification of the residue by flash column chromatography (methanol / diethyl ether 19:1) yields diethyl-(2-methylthiazol-4-yl)-methanephosphonate 10 (5.066 g, 82%) as a colourless oil. Alternatively, the product can be isolated by high vacuum distillation (b. p. 110°C / 0.25 mm) together with some starting material 9 (b. p. 70 °C / 2mm). <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ = 164.3; 153.1; 142.2; 131.4; 125.7; 118.8; 114.9; 78.7; 68.3; 35.7; 34.6; 32.9; 27.8; 27.1; 25.9; 19.2; 18.3; 18.2; 16.7; 13.9; -4.7; -4.9; -5.4.

c) (3S)-Dihydro-3-hydroxy-2(3H)-furanone [(S)-2-Hydroxy-γ-butyrolactone] 11

Dropwise *via* syringe, a solution of (5S)-(2,2-cyclohexylidene-4-oxo-1,3-dioxolan-5-yl)acetic acid [synthesized starting from L-(-) malic acid, see S. Hanessian et al., J. Org. Chem. 58, 7768 - 7781 (1993)] (15.04 g, 70.2 mmol) in 70 ml of dry THF is added to a mixture of 2.0 M BH<sub>3</sub>-DMS complex (100 ml, 200.0 mmol) and B(OCH<sub>3</sub>)<sub>3</sub> (24.2 ml, 200.0 mmol) in 175 ml of dry THF cooled at 0°C. The reaction mixture is stirred over night at room temperature and cooled to 0°C, and 70 ml of MeOH is added dropwise *via* syringe. The mixture is stirred for 1 h, and the solvent is removed under reduced pressure to afford a thick oil. This process is repeated twice with MeOH (105 ml) to afford a colourless oil. The crude product (a mixture of 11 and (5S)-(2-Hydroxyethyl)-2,2-cyclohexylidene-1,3-dioxolan-4-one) is dissolved in 175 ml of dichloromethane. p-Toluenesulfonic acid is added (1.335 g, 7.02 mmol, 0.1 eq) and the mixture is stirred for 24 h at r.t. Triethyl amine (980 µl) is added and the mixture is concentrated *in vacuo*. Purification of the residue by flash column chromatography (diethyl ether) affords (3S)-dihydro-3-hydroxy-2(3H)-furanone 11 (5.160 g, 72%) as a colourless oil. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ(ppm) = 178.2; 67.4; 65.2; 30.8

d) (S)-2-(tert-Butyldimethylsilyloxy)-γ-butyrolactone 12

Imidazole (241 mg, 3.54 mmol, 2.2 equiv) and *tert*-butyl-dimethylsilyl chloride (267 mg, 1.77 mmol, 1.1 equiv) are added to a solution of (3S)-dihydro-3-hydroxy-2(3H)-furanone 11 (164 mg, 1.61 mmol) in dimethyl formamide (1.5 ml). The mixture is stirred for 24 h at r.t. Purification of the reaction mixture by flash column chromatography (pentane / diethyl ether 10:1) affords (S)-2-(*tert*-butyldimethylsilyloxy)-γ-butyrolactone 12 (321mg, 93%) as a colourless oil. [α]<sub>D</sub><sup>20</sup> = -31.7; [α]<sub>546</sub><sup>20</sup> = -37.4 (c = 0.86, CHCl<sub>3</sub>); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ(ppm) = 175.8; 68.2; 64.7; 32.3; 25.6; 18.2; -4.8; -5.3

e) (3S)-3-(tert-Butyldimethylsilyloxy)-2-hydroxy-2-methyl-tetrahydrofuran 13

Methyl lithium (670 µl [1.11 mmol, 1.1 equiv] of a 1.65 M solution in diethyl ether) is added dropwise to a stirred solution of (S)-2-(tert-butyldimethylsilyloxy)-γ-butyrolactone **12** (218 mg, 1.01 mmol) in THF (4.0 ml) cooled to -78 °C is added dropwise. After stirring at -78 °C for 3 h, the reaction is quenched by the addition of glacial acetic acid (72 µl, 1.26 mmol, 1.25 equiv). Diethyl ether (20 ml) and saturated aqueous sodium bicarbonate solution (10 ml) are added. After stirring for 5 min the organic layer is separated and the aqueous layer is extracted with diethyl ether (2 x 20 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Crude (3S)-3-(tert-butyldimethylsilyloxy)-2-hydroxy-2-methyl-tetrahydrofuran **13** (235 mg, 93%) is obtained as a colourless crystalline solid (mixture of diastereomers) which is used for the synthesis of (S)-3,5-di-(tert-butyldimethylsilyloxy)-pentan-2-one **14** without further purification.

f) (S)-3,5-Di-(tert-butyldimethylsilyloxy)-pentan-2-one 14

Imidazole (125 mg, 1.84 mmol, 2.2 equiv) and *tert*-butyl-dimethylsilyl chloride (139 mg, 0.92 mmol, 1.1 equiv) are added to a solution of (3S)-3-(tert-butyldimethylsilyloxy)-2-hydroxy-2-methyl-tetrahydrofuran **13** (194 mg, 0.83 mmol) in dimethyl formamide (800 µl). The mixture is stirred for 24 h at r. t. Purification of the reaction mixture by flash column chromatography (pentane / diethyl ether 20:1) affords (S)-3,5-di-(tert-butyldimethylsilyloxy)-pentan-2-one **14** (226 mg, 78%) as a colourless oil.  $[\alpha]_D^{20} = -11.8$ ;  $[\alpha]_{546}^{20} = -14.1$  (c = 1.0, CHCl<sub>3</sub>); <sup>1</sup>H-NMR (200 MHz, CDCl<sub>3</sub>): δ(ppm) = 4.16 (dd, 1H); 3.8 - 3.5 (m, 2H); 2.16 (s, 3H); 1.9 - 1.7 (m, 2H); 0.92 (s, 9H); 0.88 (s, 2H); 0.06 (s, 6H); 0.04 (s, 3H), 0.03 (s, 3H)

g) (S,4E)-1,3-Di-(tert-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene 15

(see D. Schinzer et al., Chem. Eur. J. **2**, 1477 - 1482 (1996)) *n*-Butyl lithium (23.5 ml [58.7 mmol, 1.2 equiv] of a 2.5 M solution in hexanes) is added dropwise to a stirred solution of diethyl-(2-methylthiazol-4-yl)-methanephosphonate **10** (14.64 g, 58.7 mmol, 1.2 equiv) in THF (150 ml) cooled to -78 °C. After stirring at -78 °C for 1 h, a solution of (S)-3,5-di-(tert-butyldimethylsilyloxy)-pentan-2-one **14** (16.96 g, 48.9 mmol, 1.0 equiv) in 100 ml of THF is added dropwise at -78 °C. The mixture is warmed to r.t. within 12 h. The reaction is quenched with saturated aqueous ammonium chloride solution (100 ml). The organic layer is separated and the aqueous layer is extracted with diethyl ether (3 x 100 ml). The combined or-

ganic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (gradient elution with pentane / dichloromethane 4:1 -> dichloromethane -> diethyl ether -> diethyl ether / methanol 10:1) affords (S,4E)-1,3-di-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene **15** (17,07 g, 38.6 mmol, 79%) as a colourless oil and some starting material (**10** and **14**). Alternatively, the crude product obtained after extraction can be directly used in the next step.

h) (S,4E)-3-(*tert*-butyldimethylsilyloxy)-1-hydroxy-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene **16** (see Schinzer et al., Chem. Eur. J. **2**, 1477-82 (1996))

20 ml of aqueous hydrofluoric acid (40 %) at 0 °C is added to a vigorously stirred solution of (S,4E)-1,3-di-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene **15** (13.255 g, 30.0 mmol) in 120 ml of diethyl ether and 120 ml of acetonitrile. Finely ground splinters of glass (133 mg) are added and the mixture is stirred for 2 h at 0 °C and analyzed by tlc. If starting material can still be detected another portion of hydrofluoric acid (20 ml) is added and stirring is continued for 1 h. The reaction is quenched by carefully adding solid sodium bicarbonate (84.0 g, 1.0 mol) within 15 min at 0 °C. After stirring for 30 min at 0 °C water is added until the salts dissolve (the pH is adjusted to 6 - 8 by further addition of sodium bicarbonate, if necessary). The mixture is extracted with dichloromethane (4 x 200 ml). The combined organic extracts are washed with brine (100 ml), dried over magnesium sulfate, and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 4:1) affords (S,4E)-3-(*tert*-butyldimethylsilyloxy)-1-hydroxy-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene **16** (8.255 g, 84%) as a viscous, colourless oil.

i) (S,4E)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-al **17**

A solution of dimethyl sulfoxide (2,04 ml, 28.8 mmol, 2.4 equiv) in 6.0 ml of dichloromethane is added dropwise within 5 min to a stirred solution of oxalyl chloride (1.14 ml, 13.2 mmol, 1.1 equiv) in 30 ml of dichloromethane cooled to -78 °C. The mixture is stirred for 10 min at -70 °C. A solution of (S,4E)-3-(*tert*-butyldimethylsilyloxy)-1-hydroxy-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-ene **16** (3.93 g, 12.0 mmol) in 5 ml of dichloromethane is added dropwise within 5 min. The mixture is stirred for 30 min at -70 °C. The reaction is quenched by dropwise addition of triethyl amine (8.4 ml, 60.0 mmol). The mixture is warmed to r.t. within 45 min. Water (30 ml) is added and the mixture is stirred for 10 min. The organic layer is separated and the aqueous layer is extracted with dichloromethane (3 x 100 ml). The combi-

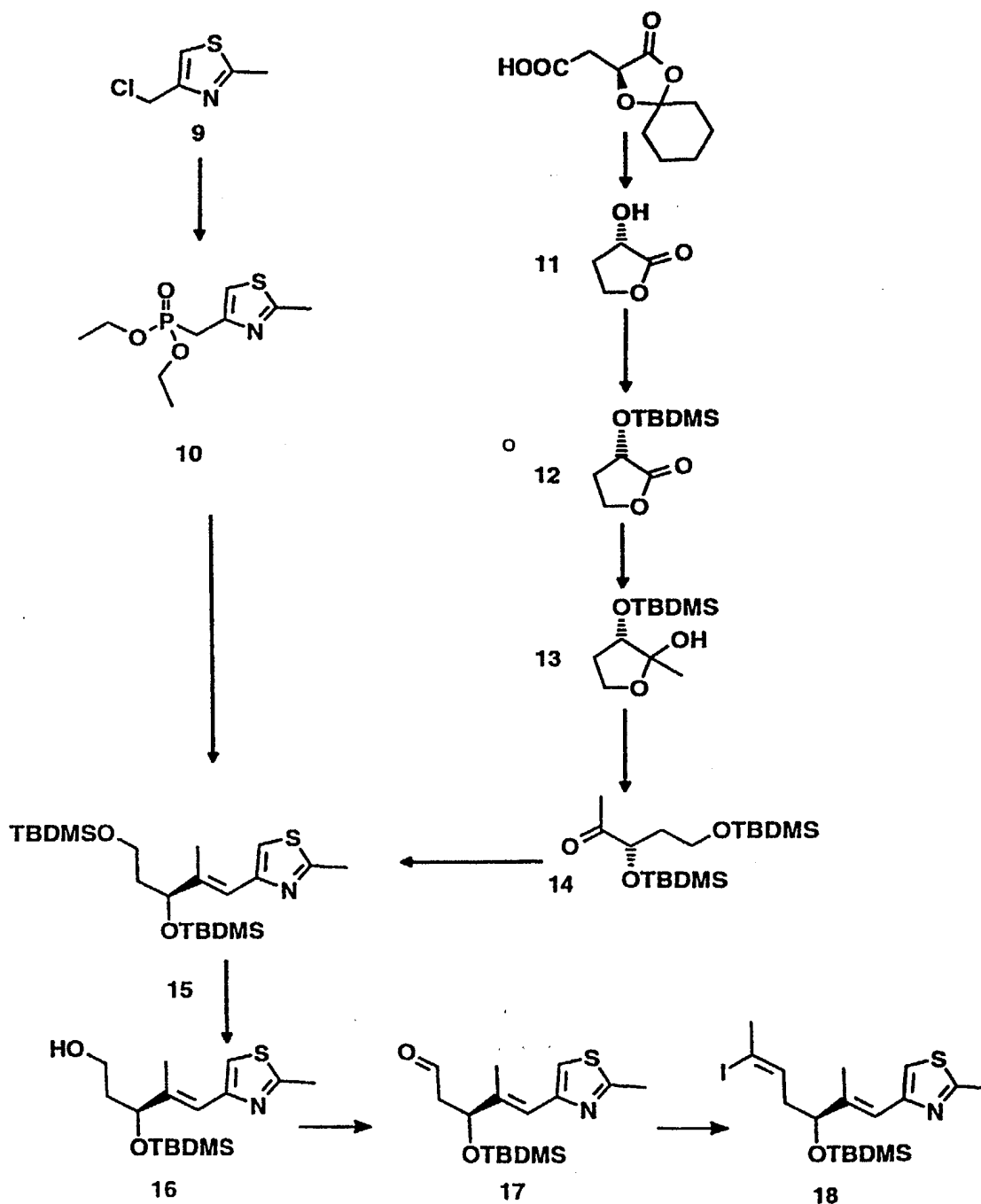
ned organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 5:2) affords (S,4E)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-al **17** (3.21 g, 82%) as a pale yellow oil.

j) (S,2Z,6E)-5-(*tert*-butyldimethylsilyloxy)-2-iodo-6-methyl-7-(2-methylthiazol-4-yl)-hepta-2,6-diene **18**

Butyl lithium (5.14 ml [12.86 mmol, 1.96 equiv] of a 2.5 M solution in hexanes) is added dropwise to a stirred suspension of ethyl triphenylphosphonium iodide (13.12 mmol, 2.0 equiv) in 60 ml of THF cooled to 0°C. The resulting clear red ylide solution is added dropwise to a rapidly stirred solution of iodine (3.163 g, 12.46 mmol, 1.90 equiv) in 90 ml of THF cooled to -78 °C. The resulting yellow suspension is stirred vigorously for 10 min at -78 °C and for 30 min at -30 to -40 °C. 11.81 ml (11.81 mmol, 1.80 equiv) of a solution of sodium hexamethyldisilazide (NaHMDS, 1.0 M in THF) is added dropwise within 10 min at -30 °C. The mixture is stirred for 15 min at -30 °C. A solution of (S,4E)-3-(*tert*-butyldimethylsilyloxy)-4-methyl-5-(2-methylthiazol-4-yl)-pent-4-en-1-al **17** (2.137g, 6.56 mmol) in 30 ml of THF is added dropwise within 10 min. The mixture is stirred for 10 min at -30 °C and quenched with saturated aqueous ammonium chloride solution (10 ml). Pentane (150 ml) is added and the mixture is filtered to a small plug of silica. The column is eluted with 400 ml of pentane / diethyl ether (4 : 1). The filtrate is concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 10:1) affords (S,2Z,6E)-5-(*tert*-butyldimethylsilyloxy)-2-iodo-6-methyl-7-(2-methylthiazol-4-yl)-hepta-2,6-diene **18** (1.640 g, 54%) as a pale yellow oil. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 164.17; 152.85; 141.50; 131.89; 118.66; 115.01; 102.09; 76.45; 43.47; 33.42; 25.58; 18.98; 17.97; 13.87; -4.90, -5.23 (-SiMe<sub>2</sub>tBu)

Alternatively, the iodoethyl phosphonium iodide that is formed as a precipitate in the first step of the above reaction sequence (upon addition of n-BuLi to ethyl phosphonium iodide) can be isolated by filtration and recrystallized from dichloromethane/THF. It is an air-stable crystalline yellow solid (m. p. ; <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>): δ = 8.1 - 7.7 m (15H); 6.3 m (1H); 2.55 dd (3H)).

Scheme 2



Preparation of 18 can then be carried out as follows:

0.600 ml of a 1M solution of NaHMDS in THF are added at  $-78^{\circ}$  to a suspension of 0.680 g of iodoethyl phosphonium iodide in 20 ml of THF. After stirring at  $-78^{\circ}$  for 30 min, the yellow



suspension is allowed to warm to  $-15^{\circ}$  over a period of 10 min, resulting in the formation of a red solution. After 20 min at  $-15^{\circ}$  the solution is again cooled to  $-78^{\circ}$  and 0.325 g of aldehyde 17 are added at this temperature. After 20 min at  $-78^{\circ}$ , the reaction is quenched by adding 5 ml of saturated aqueous  $\text{NH}_4\text{Cl}$  at  $-78^{\circ}$  and then worked up as described above.

### **3) Pd Coupling and Transformation of the Coupling Product (Scheme 5)**

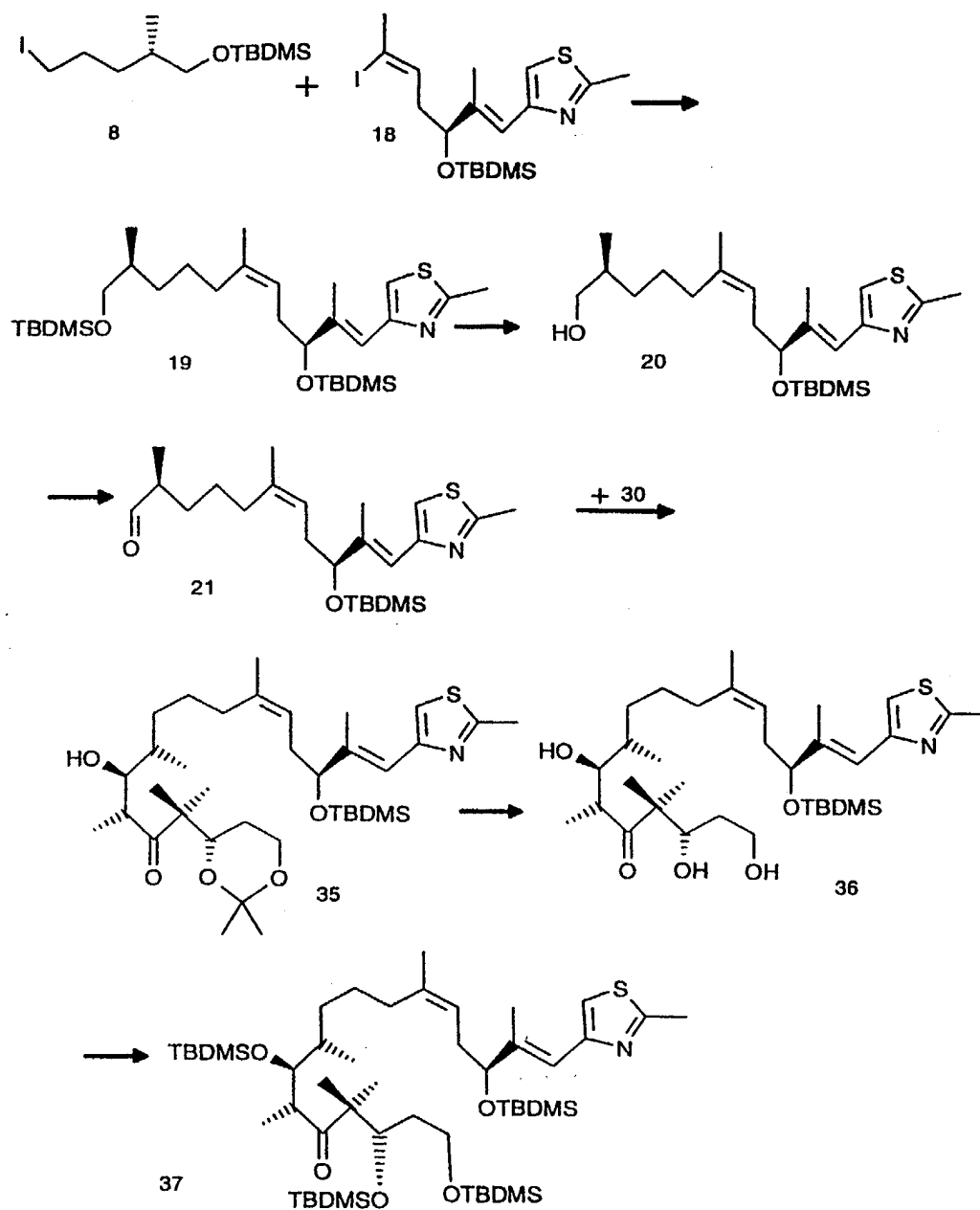
#### **a) (6S,10S,2Z,6E)-3,11-Di(*tert*-butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethyl-undeca-1,5-diene 19**

1,2-Dibromoethane (35  $\mu$ l) is added to a suspension of powdered Zn/Cu couple [J. E. McMurry, J. G. Rico: Tetrahedron Lett. **30**, 1169 - 1172 (1989)] (477 mg, 7.27 mmol, 2.3 equiv) in 11 ml of benzene under argon. The mixture is heated for a few seconds under reflux. After cooling to r.t., chlorotrimethylsilane (35  $\mu$ l) is added and the mixture is stirred for 5 min. N,N-dimethylacetamide (750  $\mu$ l) and (S)-1-iodo-5-(*tert*-butyl-dimethylsilyloxy)-4-methyl-pentane **8** (1.623 g, 4.74 mmol, 1.5 equiv) in 4.0 ml of benzene is added. The mixture is stirred for 2 h 30 min at 60 °C and analyzed by tlc. If starting material can still be detected, triethylsilyl trifluoromethanesulfonate (20  $\mu$ l) or a few mg of mercury(II) acetate (for further activation of the metal) and 750  $\mu$ l of N,N-dimethylacetamide is added, and the mixture is heated under reflux for 1 h. After cooling to r.t., Pd(PPh<sub>3</sub>)<sub>4</sub> (140 mg, 4mol-%) is added and the mixture is stirred for 5 min. A solution of (S,2Z,6E)-5-(*tert*-butyldimethylsilyloxy)-2-iodo-6-methyl-7-(2-methylthiazol-4-yl)-hepta-2,6-diene **18** (1.463 g, 3.16 mmol) in 3.0 ml of benzene is added and the mixture is stirred for 30 min at 60 °C. After cooling to r.t., the reaction is quenched with saturated aqueous ammonium chloride solution (5 ml). The organic layer is separated and the aqueous layer is extracted with methyl *tert*-butyl ether (3 x 30 ml). The combined organic layers are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 25:1) affords (6S,10S,2Z,6E)-3,11-di-(*tert*-butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethyl-undeca-1,5-diene **19** (1.458 g, 84%) as a colourless oil. Alternatively, benzene can be replaced by THF in the reaction. The yields decrease to 64%. => for spectroscopical data cf. ref. [K. C. Nicolaou et al., J. Am. Chem. Soc. **119**, 7974 - 7991 (1997)].

#### **b) (6S,10S,2Z,6E)-3(*tert*-butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethyl-undeca-1,5-dien-11-ol 20**

The synthesis is carried out according to the Nicolaou procedure, see K. C. Nicolaou et al., J. Am. Chem. Soc. **119**, 7974 - 7991 (1997) by reaction in methylene chloride:methanol (1:1, v/v) in the presence of campher sulfonic acid.

Scheme 5:



c) (6*S*,10*S*,2*Z*,6*E*)-3-(*tert*-Butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethylundeca-1,5-dien-11-al **21**

A solution of (6*S*,10*S*,2*Z*,6*E*)-3(*tert*-butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-

trimethyl-undeca-1,5-dien-11-ol **20** (306 mg, 0.7 mmol) in 5.0 ml of dichloromethane is added dropwise to a stirred solution of the Dess-Martin periodinane (386 mg, 0.91 mmol, 1.3 equiv) in 5.0 ml of dichloromethane and 73  $\mu$ l (0.91 mmol) of pyridine cooled to 0 °C. The mixture is stirred for 30 min at r.t. Diethyl ether (30 ml), pyridine (146  $\mu$ l, 1.82 mmol) and 0.5 M buffered (pH 7) aqueous sodium thiosulfate solution (10 ml) are added. The organic layer is separated off, and the aqueous layer is extracted with methyl *tert*-butyl ether (2 x 20 ml). The combined organic layers are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 5:1) affords (6*S*,10*S*,2*Z*,6*E*)-3(*tert*-butyldimethylsilyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethyl-undeca-1,5-dien-11-al **21** (295 mg, 97%) as a pale yellow oil;  $^{13}\text{C}$ -NMR:  $\delta$  = 205.2; 164.4; 153.0; 142.0; 130.6; 126.4; 118.8; 115.0; 78.7; 46.2; 34.7; 30.0; 27.3; 26.9; 25.8; 19.2; 18.2; 13.9; 13.2; -4.7; -5.0.

#### 4) The HYTRA Route to the Ethyl Ketone (Scheme 4)

(see P. Eilbracht et al., Chem. Ber. 122, 151 - 158 (1989))

##### a) Ethyl 2,2-dimethyl-3-ethyl-3-hydroxypentanoate **22**

A suspension of zinc dust (39.2 g, 0.6 mol) in 150 ml of THF and 150 ml of  $\text{B}(\text{OCH}_3)_3$  is activated with 1,2 dibromoethane (3.0 ml) and chlorotrimethylsilane (3.0 ml). Diethyl ketone (95.7 ml, 0.9 mol) is added to the activated zinc suspension. Ethyl 2-bromo-2-methylpropanoate (Fluka, Buchs, Schweiz) is added dropwise within 90 min to the mixture. The mixture is stirred at r.t. for 20 h. The reaction is quenched by addition of concentrated aqueous ammonia solution (150 ml) at 0 °C. Glycerine (150 ml) and diethyl ether (150 ml) is added and the organic layer is separated. The aqueous layer is extracted twice with diethyl ether. The combined organic layers are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by vacuum distillation affords ethyl 2,2-dimethyl-3-ethyl-3-hydroxypentanoate **22** (56.65 g, 47%) as a colourless liquid (b. p. 108 - 110 °C / 10 mbar).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 179.2; 76.2; 60.9; 50.3; 28.2; 21.6; 14.1; 8.9

##### b) Ethyl (*E*)-2,2-Dimethyl-2-ethyl-3-pentenoate **23**

Ethyl 2,2-dimethyl-3-ethyl-3-hydroxypentanoate **22** (56.64 g, 280 mmol) is heated under reflux with phosphorous pentoxide (50.4 g, 355 mmol) in benzene (200 ml) for 15 min. Benzene is distilled off. The residue is extracted with diethyl ether (3 x 100 ml) and dissolved in saturated aqueous sodium bicarbonate solution (150 ml) at 0 °C. The resulting solution is

neutralized by carefully adding sodium carbonate and extracted with diethyl ether (3 x 100 ml). The combined ethereal extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by vacuum distillation affords the title compound 23 (36.09 g, 70%) as a colourless liquid (b. p.60 - 63 °C / 3 mbar). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 177.2; 144.1; 118.5; 60.3; 48.4; 24.9; 21.7; 14.1; 13.9; 13.5

c) (E)-2,2-Dimethyl-3-ethyl-3-penten-1-ol 24

Ethyl (E)-2,2-dimethyl-3-ethyl-3-pentenoate 23 (35.58 g, 193 mmol) is added dropwise to a suspension of lithium aluminium hydride (12.1 g, 320 mmol) in 81 ml of THF. The mixture is refluxed for 3 h, stirred for 16 h at r. t. and quenched with ice. The precipitate is filtered off by suction, washed several times with diethyl ether and hydrolyzed with 1 M hydrochloric acid. The aqueous solution is extracted with diethyl ether (3 x 100 ml). The combined ethereal extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by vacuum distillation affords the title compound 24 (15.87 g, 58%) as a colourless liquid (b. p.105 - 106 °C / 30 mbar). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 145.2; 120.5; 69.7; 42.0; 24.0; 20.0; 14.2; 13.6

d) (E)-2,2-Dimethyl-3-ethyl-3-pentenal 25

A solution of dimethyl sulfoxide (18.7 ml, 260 mmol) in 80 ml of dichloromethane is added dropwise within 5 min to a stirred solution of oxalyl chloride (11 ml, 130 mmol) in 400 ml of dichloromethane cooled to -78 °C. The mixture is stirred for 10 min at -70 °C. A solution of (E)-2,2-Dimethyl-3-ethyl-3-penten-1-ol 24 (15.57 g, 110 mmol) in 60 ml of dichloromethane is added dropwise within 5 min. The mixture is stirred for 1 h at -70 °C. The reaction is quenched by dropwise addition of triethyl amine (76.3 ml, 550 mmol). The mixture is warmed to r.t. within 45 min. Water (400 ml) is added and the mixture is stirred for 10 min. The organic layer is separated off, and the aqueous layer is extracted with diethyl ether (3 x 200 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by vacuum distillation affords the title compound 25 (9.7 g, 63%) as a colourless liquid (b. p.85 - 86 °C / 28 mbar). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 203.5; 141.4; 122.6; 52.7; 24.2; 20.9; 14.1; 13.8

e) (1S)-(1,2,2-Triphenyl-2-hydroxyethyl)-(3S,E)-4,4-dimethyl-5-ethyl-3-hydroxy-5-heptenoate 26

3.20 ml (8.0 mmol) of a 2.5 M solution of *n*-butyl lithium in hexanes at -78 °C is added to a solution of diisopropylamine (1.28 ml, 8.0 mmol) in 10 ml of THF cooled to -78 °C. The LDA solution is stirred for 30 min at 0 °C and added dropwise to a solution of (*S*)-(-)-2-hydroxy-1,2,2-triphenyl acetate (1.330 g, 4.0 mmol) in 25 ml of THF at -78 °C. The mixture is stirred for 1 h at 0 °C. The resulting orange-red solution is cooled to -78 °C, and a solution of (*E*)-2,2-Dimethyl-3-ethyl-3-pentenal 25 (673 mg, 4.8 mmol, 1.2 equiv) in 5.0 ml of THF is added dropwise. The mixture is stirred for 90 min. The reaction is quenched with saturated aqueous ammonium chloride solution (30 ml). The organic layer is separated and the aqueous layer is extracted with dichloromethane (3 x 50 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 3:1) affords the title compound 26 (1.41 g, 75%, 94% de) as a colourless crystalline solid (m. p. 100 °C). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 172.2; 146.0; 144.7; 142.6; 135.6; 128.4; 128.3; 128.0; 127.8; 127.5; 127.3; 127.1; 126.3; 126.2; 120.3; 80.4; 78.9; 72.3; 44.0; 37.4; 21.9; 21.3; 20.2; 14.3; 13.6

(f) (*E*)-4,4-Dimethyl-5-ethyl-3*S*-hydroxyhept-5-enoic acid 27

Potassium hydroxide (163 mg, 2.5 mmol) is added to a solution of the ester (1.182 g, 2.5 mmol) in 29 ml of methanol and 8.3 ml of water. The mixture is heated under reflux for 2 h, cooled to r. t. and concentrated *in vacuo*. The resulting suspension is filtered by suction. The solid is washed with 50 ml of water. The combined aqueous layers are extracted with dichloromethane (2 x 50 ml) to remove traces of (*S*)-2,2,1-triphenyl ethanediol. The aqueous solution is cooled to 0 °C and acidified to pH 2.5 by dropwise addition of 6 N hydrochloric acid with vigorous stirring. The clear solution is saturated with solid sodium chloride and extracted with ethyl acetate (5 x 50 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. After complete evaporation, (*E*)-4,4-dimethyl-5-ethyl-3*S*-hydroxyhept-5-enoic acid 27 (442 mg, 88%) is obtained as a colourless crystalline solid. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 178.5; 145.8; 121.0; 72.2; 44.0; 36.7; 22.5; 21.8; 20.4; 14.3; 13.7]

g) (*S*)-(*E*)-4,4-Dimethyl-5-ethyl-5-heptene-1,3-diol 28

Lithium aluminium hydride (1.325 g, 35.0 mmol, 7.0 equiv) is added portionwise to a refluxing solution of (1*S*)-2,2,1-triphenyl-2-hydroxyethyl (3*S*,*E*)-4,4-dimethyl-5-ethyl-3-hydroxy-5-heptenoate 26 (2.364 g, 5.0 mmol) in diethyl ether (50 ml) within a period of 2 h. Refluxing

is continued for 30 min. After cooling to 0 °C, the reaction is quenched dropwise with 1.35 ml water and 1.35 ml of aqueous NaOH (15%). Diethyl ether (40 ml) and water (2.0 ml) is added. The mixture is stirred for 1 h at r. t. until a white precipitate forms which is filtered off by suction through a small plug of celite. The precipitate is washed with diethyl ether (4 x 40 ml). The filtrate and the washings are combined and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 2:1) affords (S)-2,2,1-Triphenyl-ethane-1,2-diol (922 mg, 99%) as a colourless, crystalline solid and (S)-(E)-4,4-Dimethyl-5-ethyl-5-heptene-1,3-diol **28** (836 mg, 90%) as a colourless oil. <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>): δ = 146.2; 121.1; 75.8; 62.6; 44.4; 32.7; 22.8; 21.1; 20.1; 14.3; 13.6

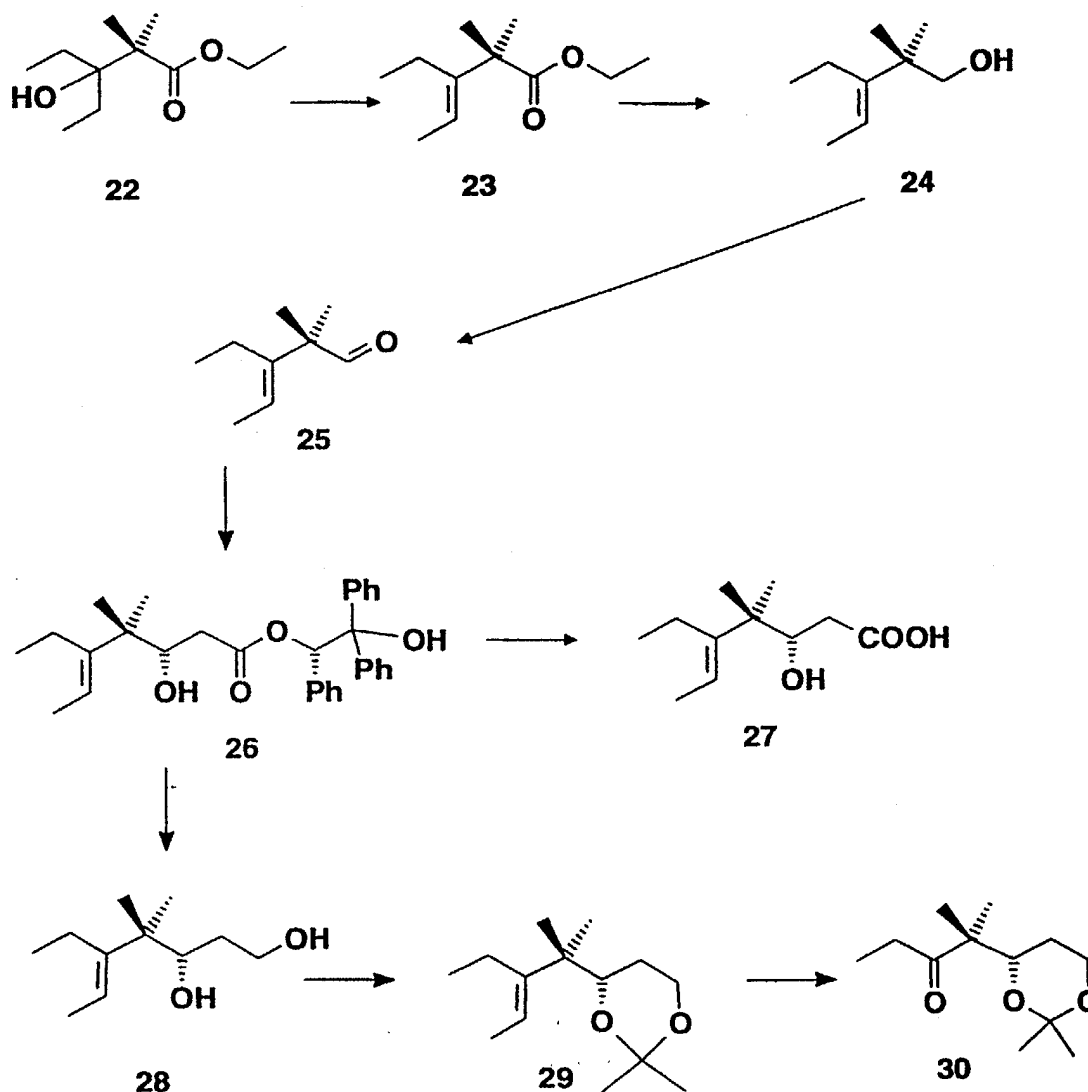
h) (S)-(E)-4-(2,2-Dimethyl-[1,3]dioxan-4-yl)-3-ethyl-2-methyl-pent-3-ene **29**

Anhydrous copper sulfate (478 mg, 3.0 mmol, 1.5 equiv), p-toluenesulfonic acid monohydrate (76 mg, 0.4 mmol, 0.2 equiv), and pyridine (24 µl, 0.3 mmol, 0.15 equiv) are added to a solution of (S)-(E)-4,4-dimethyl-5-ethyl-heptane-1,3-diol **28** (372 mg, 2.0 mmol) in acetone (30 ml). The mixture is stirred for 24 h at r. t. Saturated aqueous sodium bicarbonate solution (40 ml) is added, and the aqueous layer is extracted with diethyl ether (4 x 60 ml). The combined organic extracts are dried over magnesium sulfate and carefully concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 40:1) affords the title compound **29** (812 mg, 90%) as a colourless oil. <sup>13</sup>C-NMR (50 MHz, CDCl<sub>3</sub>): δ = 146.2; 119.3; 98.3; 74.2; 60.4; 42.9; 29.9; 26.2; 24.3; 21.2; 19.2; 14.4; 13.7

i) (S)-2(2,2-Dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one **30** ("ethyl ketone")

Ozone in oxygen is bubbled through a stirred solution of (S)-(E)-4-(2,2-dimethyl-[1,3]dioxan-4-yl)-3-ethyl-4-methyl-pent-2-ene **29** (226 mg, 1.0 mmol) in dichloromethane (40 ml) at -78 °C until the blue colour of ozone persists. Triphenyl phosphine (262 mg, 1.2 equiv) is added. The reaction mixture is warmed to r.t. within 4 h and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 5:1) affords (S)-2(2,2-dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one **30** (182 mg, 85%) as colourless crystals. <sup>13</sup>C-NMR (CDCl<sub>3</sub>) δ = 213.2; 98.4; 74.2; 59.8; 50.; 31.7; 30.0; 25.6; 21.0; 19.4; 19.0; 8.2.

Scheme 4



#### 5. Alternative Synthesis of compound 30 (Scheme 3):

##### a) Compound 31:

Under an Ar atmosphere, 336 ml of triethyl borane are added slowly to 2.5 l of hexane at room temperature (ca. 25 min). To this solution, 187 ml of  $\text{CF}_3\text{SO}_3\text{H}$  are added under cooling. After rinsing the dropping funnel with 180 ml of dichloromethane, the mixture is slowly warmed to 40° until gas evolution ceases (ca. 70 min). It is then cooled and a solution of



459 g of (2R)-N-acetylbornane-10,2-sultam (W.Oppolzer et al., *Tetrahedron Lett.* **1992**, *33*, 2439) in 4 l of dichloromethane is added at 0°-2° over a period of 20 min followed by a solution of 382 ml of diisopropylethyl amine (Hünig's base) in 1.5 l of dichloromethane (also at 0°-2°; ca 20 min). The reaction mixture is then cooled to -75° and a solution of 329 g of 2,2-dimethyl-3-oxo-pentanal (K. C. Nicolaou et al., *J. Am. Chem. Soc.* **1997**, *119*, 7974) in 300 ml of dichloromethane is added at the same temperature over a period of 35 min. After an additional 1.5 h at -70° - -75°, the reaction is quenched by addition of 400 ml of THF/water 3/1 followed by 3.5 l of saturated aqueous NH<sub>4</sub>Cl. The solution is then concentrated and diluted with 2l of ethyl acetate plus 2 l of water, and the organic layer is separated off. The remaining aqueous solution is extracted three times with 2 l of ethyl acetate, respectively, and the combined organic extracts are washed 6 times with 1 l of water and then once with 1 l of brine. Drying over Na<sub>2</sub>SO<sub>4</sub> and evaporation of solvent gives a semi-crystalline yellow residue which is then recrystallized twice from ethylacetate/hexane to yield 316 g of **31** as a single diastereoisomer (white crystals). M. p.: 121 - 122 °C. MS (C<sub>19</sub>H<sub>31</sub>NO<sub>5</sub>S; 385.52): 386 [M+H]. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 4.3 m (1H); 3.85 m (1H); 3.45 dd (2H); 3.25 m (1H); 2.9 - 2.65 m (2H); 2.55 q (2H).

**b) Compound 32:**

To a solution of 409 g of compound **31** in 3 l of dichloromethane, 185 ml of 2,6-lutidine are added, followed by a solution of 292 ml of t-butyl-dimethylsilyl triflate in 200 ml of dichloromethane (both additions at approximately -75°). The reaction mixture is stirred at -75° for 2.5h and then allowed to warm to room temperature over night. Then, the mixture is extracted three times with 1 l of water, respectively, the combined aqueous extracts are re-extracted twice with each time 1 l of dichloromethane, and the combined organic extracts are finally evaporated to dryness. The residue is recrystallized from ethanol/water to yield 485 g of **32** as white crystals. M. p.: 87 - 89 °C. MS (C<sub>19</sub>H<sub>45</sub>NO<sub>5</sub>SSi; 499.78): 500 [M+H]. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 4.75 m (1H); 3.8 m (1H); 3.4 dd (2H); 2.95dd (1H); 2.75 dd (1H); 2.5 q (2H); 0.8 s (9H).

**c) 3(S)-(tert-Butyl-dimethyl-silyloxy)-4,4-dimethyl-5-oxo-heptanoic acid 33:**

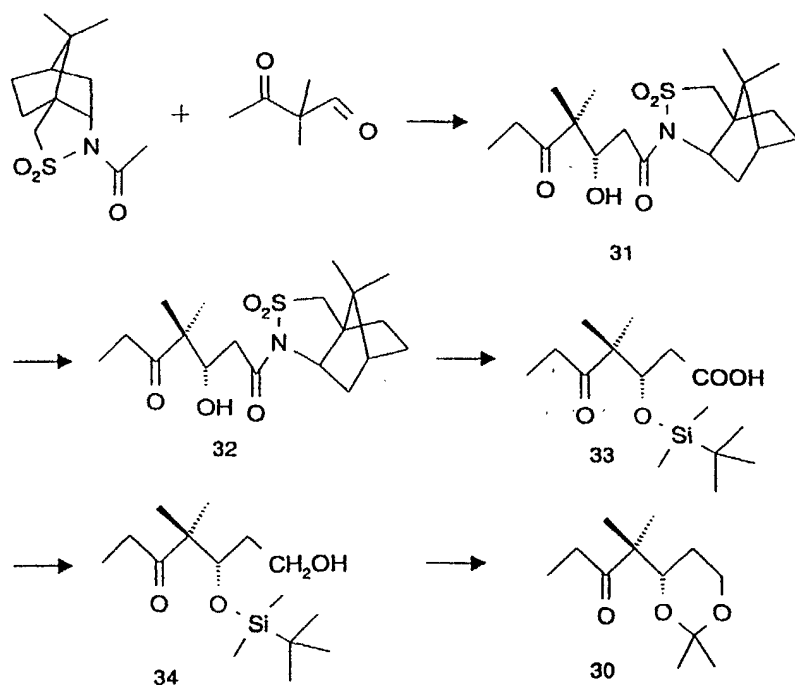
To a solution of 10 g of compound **32** in 100 ml of THF/water 4/1, 0.772 g of LiOH are added, followed by 3.37 ml of 30% aqu. H<sub>2</sub>O<sub>2</sub>. After 7 h stirring at room temperature, 3.78 g of Na<sub>2</sub>SO<sub>3</sub> are added to the mixture and the THF is removed by evaporation. 50 ml of ethyl

acetate are added to the remaining aqueous suspension and the pH is adjusted to 6 by addition of 1 N HCl. The organic layer is then removed and the aqueous solution is extracted twice with ethyl acetate. The combined organic extracts are evaporated and the residue is suspended in 50 ml of hexane. After stirring at 0° C for 1 h the mixture is filtered, the filtrate evaporated and the residue purified by Flash Chromatography in dichloromethane/MeOH 97/3 → 95/1 to yield 4.58 g of **33** as an oil. <sup>1</sup>H-NMR (CDCl<sub>3</sub>): δ = 4.45 m (1H); 3.6 - 3.4 m (3H); 2.3 dd (1H); 1.15 s (3H); 1.05 s (3H); 1.00 t (3H); 0.85 s (9H).

d) 5(S)-(tert-Butyl-dimethyl-silyloxy)-7-hydroxy-4,4-dimethyl-heptan-3-one **34**:

1.017 ml of trimethyl borate, followed by 0.607 ml of BH<sub>3</sub>·x Me<sub>2</sub>S, are added to a solution of 0.689 g of compound **33** in 20 ml of THF at 0°. The reaction mixture is stirred at 0° for 2h and at 15° for 6h. It is then cooled to 0°, 3 ml of water are added dropwise and the mixture is stirred for 10 min. The solvents are subsequently evaporated and the residue is re-evaporated three times after addition of methanol and then purified by flash chromatography using dichloromethane/ ether 98/2 to give 0.71 g of **34** as an oil. MS (C<sub>15</sub>H<sub>32</sub>O<sub>3</sub>Si; 288): 271 [M - OH]; 231 [M - t-butyl].

Scheme 3:



e) (S)-2(2,2-Dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one 30:

A solution of 0.200 g of compound **34** in 5 ml of acetone/ $\text{CF}_3\text{COOH}$  is heated to  $35^\circ$  for 18h. Triethyl amine (1 ml) is then added to the mixture at  $0^\circ$  followed by 20 ml of diethyl ether. The solution is then three times extracted with 10 ml of water each, dried, and the solvent evaporated. FC of the residue in hexane/ether 3/1 (+ 1% of triethyl amine) gives 0.118 g of **30**. MS ( $\text{C}_{12}\text{H}_{22}\text{O}_3$ ; 214): 215 [M+H].  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ ):  $\delta = 4.05 - 3.80$  m (3H); 2.5 q (2H); 1.40 s (3H); 1.30 m (includ. s) (4H); 1.10 s (3H); 1.00 s (3H); 0.95 t (3H).

6) The Aldol Reaction and the Final Steps to of the Formal Total Synthesis of Epothilone B (Scheme 5)

a) The Aldol Reaction to yield compound 35

A solution of (S)-2(2,2-Dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one **30** (64 mg, 0.3 mmol) in THF (500  $\mu\text{l}$ ) is added dropwise at  $-78^\circ\text{C}$  to a freshly prepared solution of LDA [*n*-BuLi (118  $\mu\text{l}$ , 2.5 m solution in hexanes, 0.294 mmol, 0.98 equiv) is added to a solution of diisopropylamine (41.6  $\mu\text{l}$ , 0.294 mmol) in THF (500  $\mu\text{l}$ ) at  $0^\circ\text{C}$ . The mixture is stirred for 30 min at  $0^\circ\text{C}$ .]. Then, the solution is stirred for 1 h at  $-78^\circ\text{C}$ . A solution of (6*S*,10*S*,2*Z*,6*E*)-3-(*tert*-butyldimethyl-silyloxy)-1-(2-methylthiazol-4-yl)-2,6,10-trimethyl-undeca-1,5-dien-11-al **21** (65 mg, 0.15 mmol, 0.5 equiv) in THF (600  $\mu\text{l}$ ) is added dropwise, and stirring is continued for 20 min at  $-78^\circ\text{C}$ . The mixture is quenched by dropwise addition of saturated aqueous ammonium chloride solution (2 ml). The organic layer is separated and the aqueous layer is extracted with diethyl ether (3 x 5 ml). The combined organic extracts are dried over magnesium sulfate and concentrated *in vacuo*. Purification of the residue by flash column chromatography (pentane / diethyl ether 10:1, then 5:1) affords 83 mg (85 %) of **35** as colourless oil. Major diastereoisomer:  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ ):  $\delta = 222.81$ ; 164.27; 153.28; 142.49; 136.94; 121.44; 118.65; 114.89; 98.45; 79.08; 74.74; 74.38; 59.89; 51.60; 41.28; 35.42; 35.32; 33.04; 32.40; 29.76; 25.85; 25.24; 25.15; 23.51; 21.55; 19.19; 19.03; 18.58; 18.24; 15.35; 13.92; 9.31; -4.65; -4.93

b) Triol compound 36

PPTS (6.0 mg, 24  $\mu\text{mol}$ , 0.6 equiv) is added to a solution of the ANTICRAM aldol product **35** (26 mg, 0.04 mmol) in methanol (500  $\mu\text{l}$ ). The mixture is stirred for 22 h. Another portion of PPTS (4.0 mg, 16  $\mu\text{mol}$ , 0.4 equiv) is added and stirring is continued for 50 h. The sol-

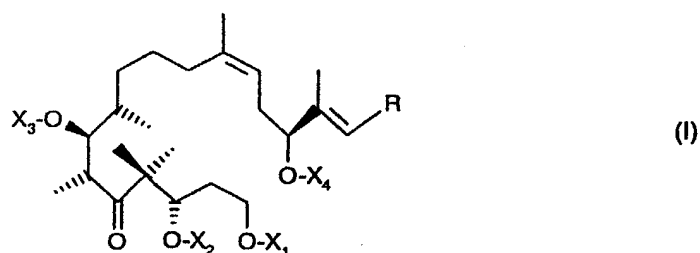
vent is removed *in vacuo* and the residue is purified by flash column chromatography with diethyl ether. The triol **36** (21 mg, 86 %) is obtained as a colourless oil.  $^{13}\text{C}$ -NMR ( $\text{CDCl}_3$ )  $\delta$  = 223.3; 154.5; 153.1; 142.7; 136.8; 121.6; 118.7; 114.8; 79.2; 76.3; 74.4; 62.1; 52.7; 41.1; 35.6; 35.4; 32.8; 32.5; 32.3; 25.8; 25.1; 23.5; 21.6; 19.1; 18.5; 18.2; 15.5; 13.8; 10.1; -4.0; -4.3.

c) Tetrakis Silyl Ether **37** (compound of formula I wherein each of  $X_1$  to  $X_4$  is *tert*-butyldimethylsilyl and R is 2-methylthiazol-4-yl)

2,6-lutidine (29  $\mu\text{l}$ , 247.5  $\mu\text{mol}$ , 2.5 equiv) is added to a solution of the triol **32** (20.0 mg, 33  $\mu\text{mol}$ ) in dichloromethane (200  $\mu\text{l}$ ). The mixture is cooled to  $-50^\circ\text{C}$  and *tert*-butyl-dimethylsilyltrifluoromethanesulfonate (34  $\mu\text{l}$ , 148.5  $\mu\text{mol}$ , 1.5 equiv) is added. The mixture is warmed  $0^\circ\text{C}$  and stirring is continued for 2 h at  $0^\circ\text{C}$ . The solvent is removed *in vacuo* and the residue is purified by flash column chromatography (pentane / diethyl ether 20:1). The tetrakis silyl ether **33** (30 mg, 95%) is obtained as a colourless oil.  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 218.25; 164.27; 153.29; 142.49; 136.75; 121.56; 118.68; 114.90; 78.99; 77.45; 74.04; 60.99; 53.66; 45.05; 38.95; 38.11; 35.34; 32.57; 31.04; 29.70; 26.24; 26.12; 25.97; 25.85; 24.50; 23.53; 19.40; 19.22; 18.52; 18.30; 18.24; 18.13; 17.56; 15.20; 13.93; -3.65; -3.67; -3.75; -3.98; -4.64; -4.92; -5.22; -5.25

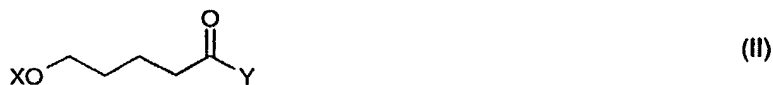
What is claimed is:

1. A method for the preparation of a compound of the formula I,



wherein R is a heterocyclyl moiety and X<sub>1</sub>, X<sub>2</sub>, X<sub>3</sub> and X<sub>4</sub> are, independently of each other, protecting groups, characterized in that

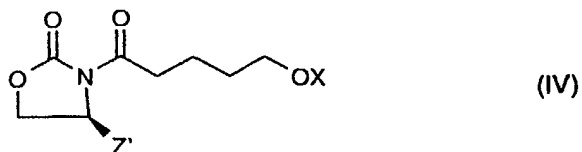
(I) a compound of the formula II



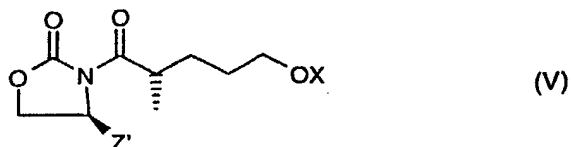
wherein Y is the radical of an organic or inorganic acid devoid of its dissociable hydrogen, and X is a protecting group as described above for X<sub>1</sub> to X<sub>4</sub>, especially benzyl; is reacted with an oxazolidone of the formula III



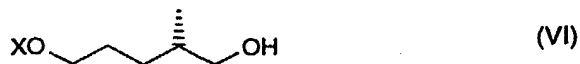
wherein Z' is lower alkyl or phenyl-lower alkyl in an appropriate solvent either (i) in the presence of a strong base, especially methyl magnesium bromide, and then of an appropriate tertiary amino base, such as 4-dimethylaminopyridine; or (ii) in the presence of an alkalimetal alkylid; at low temperatures, yielding a compound of the formula IV,



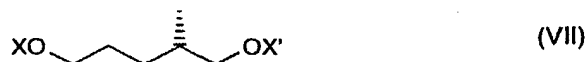
wherein X and Z' have the meanings given above; (IV) is then C-methylated to yield a compound of the formula V,



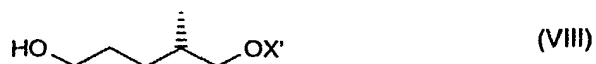
wherein X and Z' are defined as above; from that compound, then a compound of the formula VI,



wherein X is as given above is set free by reductive cleavage; then, a protecting group X' selected from the protecting groups mentioned above for X<sub>1</sub> to X<sub>4</sub>, but different from X in formula VI, is introduced at the free hydroxy group that allows that the protecting group X in the compound of formula VI can be cleaved off without affecting the newly introduced protecting group to yield a bis-protected compound of the formula VII,



with X and X' as described above; from this compound, then the protecting group X is cleaved off under appropriate conditions to yield a compound of the formula VIII,



with X' as defined for the compound of the formula VII; that compound VIII is then reacted with a halogenide of an organic sulfonic acid to yield the corresponding sulfonic acid ester of the formula IX,



wherein Q is organic sulfonyl, and that sulfonyl ester is then reacted with a metal iodide to yield the corresponding iodide compound of the formula X,



with X' as defined above; this constituting the first of three intermediates for the convergent synthesis of the compound of the formula I;

in parallel to that sequence of reactions,

a) a compound of the formula XI,



wherein R is as described under formula I and Hal is halogen is reacted with a tri-alkyl phosphite to yield a phosphonate compound of the formula XII,



wherein R is as defined under formula I and each of A is alkyl;

independently, (5S)-(2,2-cyclohexylidene)-4-oxo-1,3-dioxolane is reacted with  $\text{BH}_3\text{-Me}_2\text{S}$  complex and  $\text{B}(\text{OCH}_3)_3$  and methanol to yield 3(S)-dihydro-3-hydroxy-2(3H)-furanone (compound 11 in reaction scheme 2); that is then protected by introduction of a protecting group  $\text{X}_4$  to yield a compound of the formula XIII,



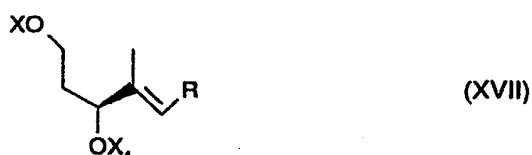
wherein  $\text{X}_4$  is a protecting group; the compound of formula XIII is then reacted with an methyl metal or methyl metal derivative to the novel compound of the formula XIV,



wherein  $\text{X}_4$  is as defined under formula XIII; the compound of formula XIV is reacted with a further reagent capable of introducing a protecting group yielding a compound of the formula XV,



wherein X and X<sub>4</sub> are a protecting group, which compound is then reacted with a phosphonate compound of the formula XII given above in the presence of an strong base yielding a compound of the formula XVII,



wherein X and X<sub>4</sub> are as defined under formula XIII and R is as defined under formula I; the compound of the formula XVII is then deprotected partially under appropriate conditions to give a compound of the formula XIX,

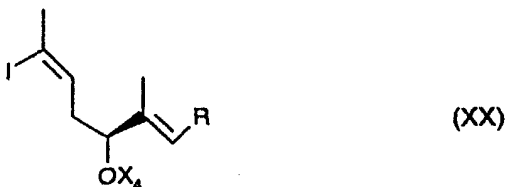


wherein the moieties X<sub>4</sub> and R are as defined under formula XVII; the compound of the formula XXVIII is oxidized selectively to the corresponding aldehyde of the formula XIX,



wherein R and X<sub>4</sub> are as defined under formula XVII, which is then, by reaction with an alkyl alkalinemetal and iodine in the presence of triphenylphosphonium iodide (either with isolation of the iodoethyl phosphonium iodide or in a one pot synthesis), and subsequent addition of a different or the same base as above, especially sodium hexamethyldisialazide, converted into a compound of the formula XX,



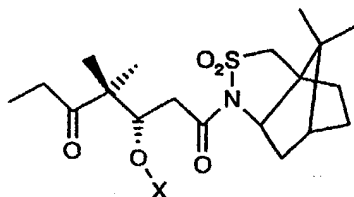


wherein R and X<sub>4</sub> are as defined under formula XVII; the compound of the formula XX being the second of the three intermediates for the convergent synthesis of the compound of the formula I;

the third intermediate for the convergent synthesis being manufactured by one of the two ways (a) and (b) described hereinafter:

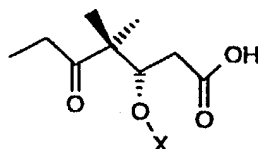
(a) diethylketon is reacted in the presence of activated zinc dust in the presence of B(OCH<sub>3</sub>)<sub>3</sub> with ethyl 2-bromo-2-methylpropanoate to ethyl 2,2-dimethyl-3-ethyl-3-hydroxy-pentanoate 22, which is then reacted with a dehydrating agent to ethyl (E)-2,2-dimethyl-2-ethyl-3-pentenoate 23; which is then reacted in the presence of an appropriate complex hydride to E-2,2-dimethyl-3-ethyl-3-penten-1-ol 24; this is then oxidised with an appropriate oxidant, to (E)-2,2-dimethyl-3-ethyl-3-pentenal 25, which is then reacted with (S)-(-)-2-hydroxy-1,2,2-triphenyl acetate in the presence of a strong base to (1S)-2,2,1-triphenyl-2-hydroxyethyl-(3S,E)-4,4-dimethyl-5-ethyl-3-hydroxy-5-heptenoate 26; that compound is transformed, by reaction with an appropriate complex hydride, into (S)-(E)-4,4-dimethyl-5-ethyl-5-heptene-1,3-diol 28, which is then converted, by reaction with acetone in the presence of anhydrous copper sulfate, a strong organic acid, and a tertiary nitrogen base, to give (S)-(E)-2,2-dimethyl-[1,3]dioxan-4-yl)-3-ethyl-2-methyl-pent-3-ene 29; this compound is then converted to the third intermediate for the convergent synthesis, the ethyl ketone (S)-2-(2,2-dimethyl-[1,3]dioxan-4-yl)-2-methyl-pentan-3-one 30 by ozonolysis; or, alternatively,

(b) 30 can be obtained by reaction of (2R)-N-acetylbornane-10,2-sultam in the presence of a dialkylborane triflate or dialkylborane chloride and after addition of a tertiary nitrogen base, with 2,2-dimethyl-3-oxo-pentanal that leads to the sultam product 31, which is then reacted, in the presence of a tertiary nitrogen base, with a reagent appropriate for the introduction of a protecting group to give a compound of the formula XXI



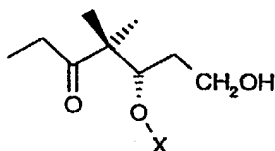
(XXI)

wherein X is a protecting group; the compound of formula XXI is then converted into the corresponding free acid of the formula XXII by reaction with an appropriate aqueous base



(XXII)

wherein X is as defined under formula XXI; the compound of formula XXII is then reduced to the corresponding alcohol of the formula XXIII

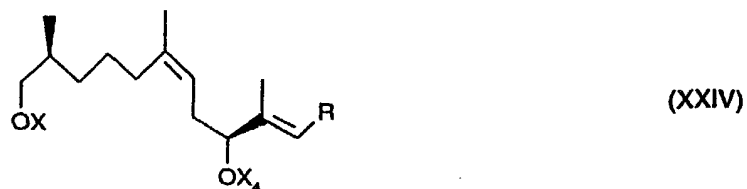


(XXIII)

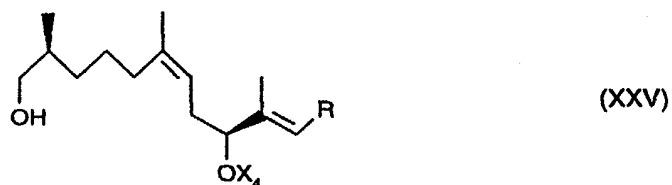
wherein X is as defined under formula XXI, and finally that compound is deprotected and transformed into compound **30** by reaction in acetone/acid, such as acetone/trifluoroacetic acid;

the compound **30** being the third intermediate for the convergent synthesis of the compound of the formula I;

and, in a next step, first the two intermediates of the formulae X and XX are coupled by reaction of the compound of the formula X with a suspension of powdered Zn/Cu couple in the presence of an activator, in the presence of halotrialkylsilane, and then addition of Palladium-tetrakis(triphenylphosphin) in an appropriate solvent, and addition of the compound of formula XX, yielding a compound of the formula XXIV,



wherein X and X<sub>4</sub> each are a protecting group and R is as defined under formula I; the compound of the formula XIV is then selectively deprotected to give a compound of the formula XXV,

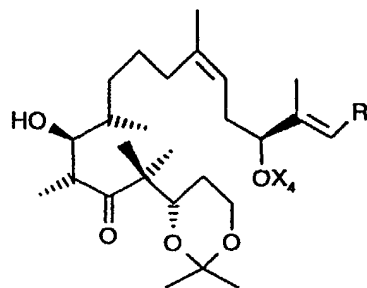


wherein X<sub>4</sub> and R are as defined under formula XXIV; the compound of the formula XXV is then oxidized with an appropriate oxidant to the corresponding aldehyde of the formula XXVI



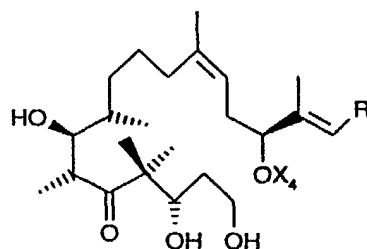
wherein X<sub>4</sub> and R are as defined under formula XXIV;

then, the third intermediate of the convergent synthesis, compound 30, is reacted with the compound of the formula XXVI in an Aldol reaction, resulting in a compound of the formula XXVII,



(XXVII)

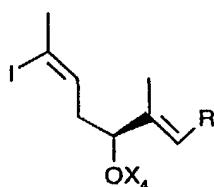
wherein  $X_4$  and R are as defined under formula I; the compound of the formula XXVII is then deprotected under removal of the acetal moiety, yielding a compound of the formula XXVIII,



(XXVIII)

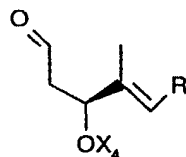
wherein  $X_4$  and R are as defined under formula I; and finally, the compound of the formula I is obtained by introduction of protecting groups  $X_1$ ,  $X_2$  and  $X_3$  with appropriate reagents.

2. A method of synthesis of a compound of the formula XX,



(XX)

wherein R is a heterocyclic moiety and  $X_4$  is a protecting group, characterized in that a compound of the formula XIX



(XIX)

wherein R and X<sub>4</sub> are as defined under formula XX, is, by reaction with an strong base and iodine in the presence of triphenylphosphonium iodide and subsequent addition of the same or another strong base as above converted into a compound of the formula XX.

3. A method of synthesis of a compound of the formula XIV,

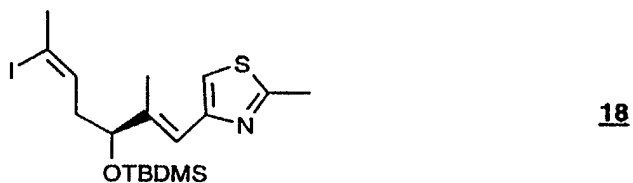


wherein X<sub>4</sub> is a protecting group, characterized in that a compound of the formula XIII,



wherein X<sub>4</sub> is a protecting group, is reacted with an methyl metal or methyl metal derivative.

4. A compound of the formula



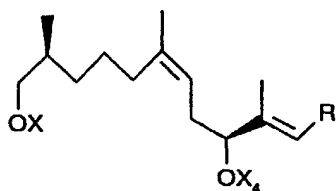
wherein TBDMS is tert-butyldimethylsilyl.

5. A compound of the formula XIV



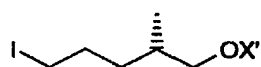
wherein X<sub>4</sub> is a protecting group other than tert-butyldimethylsilyl.

6. A method of synthesis for a compound of the formula XXIV,



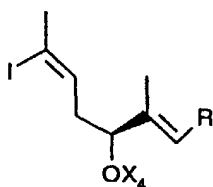
(XXIV)

wherein X and X<sub>4</sub> each are a protecting group, and R is a heterocyclyl moiety, characterized in that a compound of the formula X



(X)

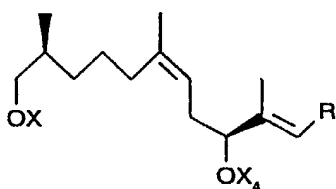
wherein X' is a protecting group, is coupled by reaction with a suspension of powdered Zn/Cu couple in the presence of an activator and of a halotrialkylsilane, and then addition of a Pd(0)-complex in an appropriate solvent, with a compound of the formula XX



(XX)

wherein X<sub>4</sub> is a protecting group and R is a heterocyclyl moiety.

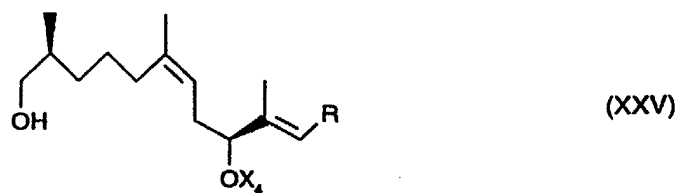
7. A compound of the formula



(XXIV)

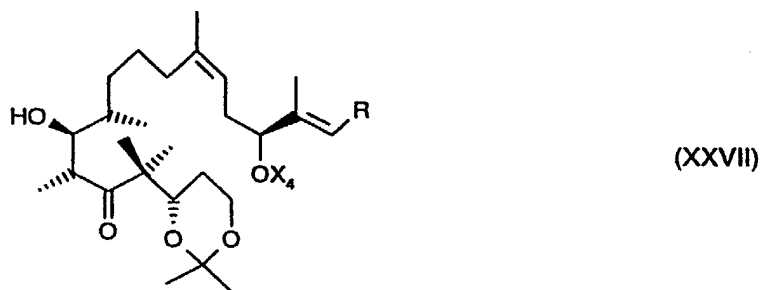
wherein X and X<sub>4</sub> each are a protecting group, and R is a heterocyclyl moiety, in the essentially pure cis-form.

8. A compound of the formula XXV,



wherein  $X_4$  is a protecting group and R is a heterocyclyl moiety in the essentially pure cis-form.

9. A compound of the formula XXVII,



wherein  $X_4$  is a protecting group and R is a heterocyclyl moiety.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 99/03354

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
IPC 6	C07D277/24	C07F7/18
C07D307/32	C07D417/06	C07D263/32
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
IPC 6	C07D	C07F
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 08849 A (NOVARTIS AKTIENGESELLSCHAFT) 5 March 1998 (1998-03-05) page 11; claims	1
A	WO 97 19086 A (GESELLSCHAFT FÜR BIOTECHNOLOGISCHE FORSCHUNG GMBH ) 29 May 1997 (1997-05-29) claims	1
-/-		
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family		
Date of the actual completion of the international search		Date of mailing of the international search report
28 July 1999		09/08/1999
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  Henry, J



## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 99/03354

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	K.C.NICOLAOU ET AL: "Total syntheses of Epothilones A and B via a macrolactonization-based strategy" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY., vol. 119, no. 34, 1997, pages 7974-7991, XP002110540 AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC., US ISSN: 0002-7863 the whole document	1
A	DIETER SCHINZER ET AL: "Studies towards the total synthesis of epothilones: asymmetric synthesis of the key fragment" CHEMISTRY - A EUROPEAN JOURNAL., vol. 2, no. 11, 1996, pages 1477-1482, XP002110541 VCH PUBLISHERS., US ISSN: 0947-6539 the whole document	1
A	K.C. NICOLAOU ET AL: "Total synthesis of oxazole- and cyclopropane-containing epothilone B analogues by the macrolactonization approach" CHEMISTRY - A EUROPEAN JOURNAL., vol. 3, no. 12, 1997, pages 1971-1986, XP002110542 VCH PUBLISHERS., US ISSN: 0947-6539 the whole document	1
P,X	DIETER SCHINZER ET AL: "Synthesis of Epothilones : Stereoselective routes to Epothilone B" SYNLETT., no. 8, 1998, pages 861-864, XP002110543 THIEME VERLAG, STUTTGART., DE ISSN: 0936-5214 the whole document	1-9
P,X	AARON BALOG ET AL: "A novel aldol condensatin with 2-methyl-4-pentenal and its application to an improved total synthesis ofvEpothilone B" ANGEWANDTE CHEMIE. INTERNATIONAL EDITION., vol. 37, no. 19, 16 October 1998 (1998-10-16), pages 26755-2678, XP002110544 VERLAG CHEMIE. WEINHEIM., DE ISSN: 0570-0833 the whole document	1-9

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# INTERNATIONAL SEARCH REPORT

Int'l. Application No.

PCT/EP 99/03354

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	MULZER J ET AL: "Easy Access to the Epothilone Family - Synthesis of Epothilone B" TETRAHEDRON LETTERS, vol. 39, no. 47, 19 November 1998 (1998-11-19), page 8633-8636 XP004140600 ISSN: 0040-4039 the whole document	1-9

# INTERNATIONAL SEARCH REPORT

information on patent family members

Int: tional Application No

PCT/EP 99/03354

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9808849 A	05-03-1998	DE 19636343 C	23-10-1997
		DE 19645361 A	30-04-1998
		DE 19645362 A	30-04-1998
		AU 2149397 A	19-03-1998
		EP 0923583 A	23-06-1999
WO 9719086 A	29-05-1997	DE 19542986 A	22-05-1997
		DE 19639456 A	26-03-1998
		EP 0873341 A	28-10-1998
		EP 0903348 A	24-03-1999